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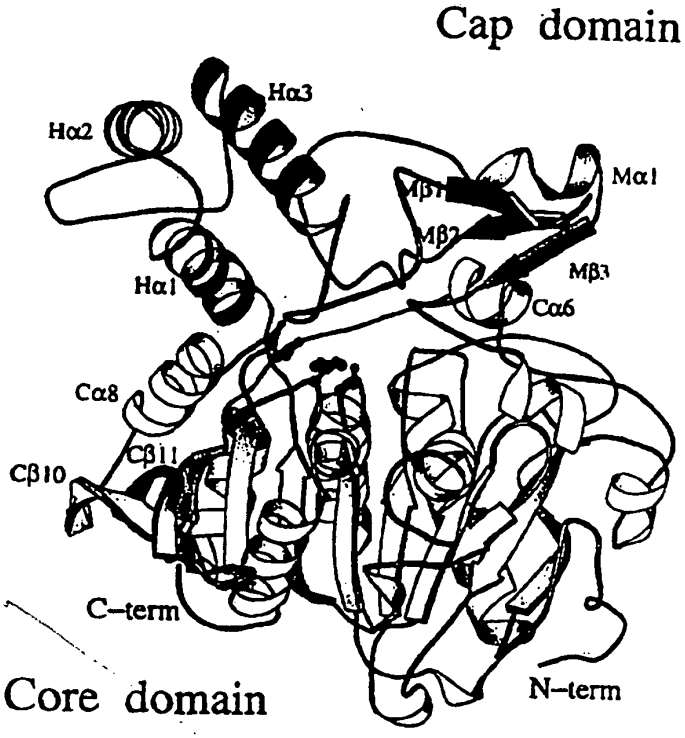
(57) Abstract

The present invention provides crystallized protective protein/cathepsin A (PPCA), a precursor thereof (pPPCA) or at least one subdomain thereof; methods for x-ray diffraction analysis to provide x-ray diffraction patterns of sufficiently high resolution for three-dimensional structure determination of the protein, as well as methods for rational drug design (RDD), based on using amino acid sequence data and/or x-ray crystallography data provided on computer readable media, as analyzed on a computer system having suitable computer algorithms.



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Protective Protein/Cathepsin A and Precursor: Crystallization, X-Ray Diffraction, Three-Dimensional Structure Determination and Rational Drug Design

Background of the Invention

Statement as to Rights to Inventions Made Under Federally-Sponsored Research and Development

Part of the work performed during development of this invention utilized U.S. Government funds. The U.S. Government has certain rights in this invention.

Field of the Invention

The present invention is in the fields of molecular biology, protein purification, protein crystallization, x-ray diffraction analysis, three-dimensional structure determination and rational drug design (RDD). The present invention provides crystallized protective protein/cathepsin A (PPCA) and its precursor (pPPCA). The crystallized PPCA or pPPCA is analyzed by x-ray diffraction techniques. The resulting x-ray diffraction patterns are of sufficiently high resolution to be useful for determining the three-dimensional structure of the PPCA or pPPCA protein, and for RDD.

Related Background Art

The human protective protein/cathepsin A (PPCA, also known as human protective protein or HPP) has been identified as the primary genetic defect underlying galactosialidosis (d'Azzo *et al.*, *Proc. Natl. Acad. Sci. U.S.A. 79*:4535-4539 (1982)), a lysosomal storage disease inherited as an autosomal recessive trait. Patients with this disorder are diagnosed as having drastically reduced β-galactosidase and neuraminidase activities in their cell lysosomes. Examples of lysosomal storage diseases are presented in Table 316-1 of Braunwald *et al., eds., Harrison's Principles of Internal Medicine,* 11th Ed., pp. 1661-1671, McGraw Hill Book Co., New York (1987); as well as Wenger *et al., Biochem. Biophys. Res. Commun. 82*:589-595 (1978); Tettamanti *et al.* eds., *Sialidases and Sialidosis. Perspectives in Inherited Metabolic Diseases*, Vol. 4, Edi. Ermes, Milano (1981), pp. 261-279 and 379-395; and van Diggelen *et. al. Lancet 2*:804(1987), which references are entirely incorporated herein by reference..

Researchers have proposed that one of PPCA's functions is to stabilize β-galactosidase and neuraminidase in a multi-enzyme complex, which complex is deficient in galactosialidosis patients (d'Azzo *et al.* (1982*), infra*; Hoogeveen *et al.* (1983*), infra*). Evidence for this protective function comes from studies showing that PPCA is taken up from the culture medium by galactosialidosis fibroblasts and that PPCA restores both β-galactosidase and neuraminidase activities to these fibroblasts (d'Azzo *et al.* (1982*), infra*).

The cDNA for PPCA directs the synthesis of a 452 amino acid precursor PPCA (pPPCA) (Figure 13) with a molecular weight of 54 kDa (Galjart *et al., Cell. 54*:755-764 (1988)). The amino acid sequences of PPCA (Figure 14) and pPPCA (Figure 13) contain two glycosylation sites (Asn 117 and Asn 305), both of which are glycosylated in cultured fibroblasts and cells over-expressing PPCA or pPPCA. pPPCA dimerizes soon after synthesis in the endoplasmic reticulum (ER) (Zhou *et al., EMBO J. 10*:404-4048 (1991)).

Lysosomal PPCA has cathepsin A/deamidase/esterase activities which are exerted *in vitro* on a specific subset of bioactive peptides. Non-limiting examples of those hydrolyzed by PPCA are: substance P and substance P-free acid; oxytocin and oxytocin-free acid; neurokinin A; angiotensin I; bradykinin (Jackman *infra.* (1990). Furthermore, the enzyme inactivates endothelin I activity in rat smooth muscle cells and normal human tissues. This activity was deficient in liver from a galactosialidosis patient (Itoh, *infra.* 1995; Jackman *et al., J. Biol. Chem. 267*:2872-2875, (1992).

Endothelins (ET-1, ET-2 and ET-3) are potent vasoconstrictors and elevate blood pressure in mammals. They also influence cell proliferation and hormone production and have been implicated in cardiovascular disorders, ranging from hypertension to stroke to ischemic heart disease (Rubanyi and Polokoff, *Pharmc. Rev. 46*:325-415 (1994)).

The three-dimensional structure of a PPCA or a pPPCA has not previously been published, which structure could delineate specific biological activities and ligands as therapeutics for PPCA-related pathologies. Accordingly, there is a need to provide three-dimensional structures of at least one PPCA, pPPCA or ligands for diagnosis or therapy of PPCA-related pathologies.

Summary of the Invention

The present invention provides methods of expressing, purifying and crystallizing a human protective protein/cathepsin A (PPCA) and its precursor, precursor protective protein/cathepsin A (pPPCA). The present invention also provides methods for obtaining crystallized PPCA or pPPCA that can be analyzed to obtain x-ray diffraction patterns of sufficiently high resolution to be useful for three-dimensional structure determination of the protein.

The x-ray diffraction patterns can be either analyzed directly to provide the three dimensional structure (if of sufficiently by high resolution), or atomic coordinates for the crystallized PPCA or pPPCA, as provided herein, can be used for structure determination. The x-ray pattern/diffraction patterns obtained by methods of the present invention, and provided on computer readable media, are used to provide electron density maps. The amino acid sequence is also useful for three-dimensional structure determination. The data is then used in combination with phase determination (*e.g.*, using multiple isomorphous replacement (MIR) molecular replacement techniques) to generate electron density maps of a PPCA or a pPPCA, using a suitable computer system.

The electron density maps, provided by analysis of either the x-ray diffraction patterns or working backwards from the atomic coordinates, provided herein, are then fitted using suitable computer algorithms to generate secondary, tertiary and/or quaternary domains of a PPCA or a pPPCA, which domains are then used to provide an overall three-dimensional structure, as well as expected binding and active sites of the PPCA or pPPCA. pPPCA has some of the active and binding sites of PPCA , except for changes in structure due to the presence of the portion of the pPPCA which is deleted during maturation to PPCA (*e.g.*, residues 285-298 of Figure 13).

Structure determination methods and computer systems are also provided by the present invention for rational drug design (RDD). These RDD methods use computer modeling programs to find potential ligands that are calculated to associate with, or bind to, sites or domains of a PPCA or a pPPCA. Potential ligands are then screened for modulating or binding activity. Such screening methods can be selected from assays for at least one PPCA-specific structural feature or biological activity, preferably as associated with a PPCA- or pPPCA-related pathology, *e.g.*, *protective activity* (*e.g.*, modulation of β-galactosidase activity and neuraminidase (NA) activity); and *peptide or enzyme modulating activity* (*e.g.*, of endothelin I (serine carboxypeptidase), neuropeptides, cathepsin A, and the like), according to known assays. The resulting ligands provided by methods of the present invention are synthesized and are useful for treating, inhibiting or preventing at least one of PPCA related pathology in a mammal.

Other objects of the invention will be apparent to one of ordinary skill in the art from the following detailed description and examples relating to the present invention.

Brief Description of the Figures

Figure 1: is a schematic ribbon diagram of the PPCA monomer (monomer 1), where Secondary structure assignments are according to DSSP (Kabsch and Sander, *Biopolymers 22*:2577-2637 (1983)). The 'core' domain is shown in yellow. The 'cap' domain consists of a 'helical' subdomain, in red, and a 'maturation' subdomain, in orange. The catalytic triad Ser 150, His 429 and Asp 372 (from right to left) is shown by small green spheres. (Figure generated using MOLSCRIPT (Kraulis, *J. Appl. Cryst. 24*:946-950 (1991))).

Figure 2 is stereo diagram is presented of the C$^{\alpha}$. trace of the PPCA monomer 1 with numbering of selected residues. The residues forming the α-helices and β-strands are as follows according to DSSP:

Core domain: Cβ1 (21-27); Cβ2(32-39); Cβ3(50-54); Cα1(63-67) Cβ4(73-75); Cβ5(82-84); Cβ6(94-98); Cα2(118-135); Cβ7(144-149); Cα3(152-163); Cβ8(171-177); Cα4(307-313); Cα5(316-321); Cα6(336-341); Cα7(350-359); Cβ9(363-369); Cα8(377-386); Cβ10(391-401); Cβ11(407-416); Cβ12(419-424); Cα9(431-434); Cα10(436-447);

Cap domain: Hα1(183-196); Hα2(202-212); Hα3(226-240); Mβ1(261-264); Mβ2(267-270); Mα1(290-293); Mβ3(296-299). Note that for monomer 2 the secondary structure assignments in the cap domain are slightly different than in monomer 1. Residues in Hβ1 are in a region of poor density and Mα1 is an extended coil. (Figure generated using MOLSCRIPT (Kraulis (1991), *infra*).

Figure 3 shows the density for the disulfide bridges Cys 212-Cys 228 and Cys 213-Cys 218 is presented as revealed in the SigmaA weighted $2mF_O$-DF_C electron density map (Read, *Acta Crystallogr. A 42*:140-149 (1986)) calculated from the model refined to 2.2 Å; the map has been contoured at 1σ. (Figure drawn with the O computer program (Jones, *Acta Crystallogr. A47*:110-119 (1991))).

Figure 4 is stereo diagram is presented of the superimposed C^α traces from the two crystallographically independent PPCA monomers forming the dimer. Monomer 1 is in blue, monomer 2 is in red. Residues referred to in the text are labeled. Residues 259 and 260 have not been incorporated in the model of monomer 2, since no electron density was observed for them. Note the tremendous difference in conformation of the excision peptide located in the upper right corner of the proteins. (Figure generated by MOLSCRIPT (Kraulis (1991), *infra*)).

Figure 5 is a schematic ribbon diagram is presented of the PPCA dimer viewed approximately along the two-fold axis. For monomer 1, the core domain is yellow while the cap domain consists of a helical subdomain in red and a maturation subdomain in orange. For monomer 2, the core domain is green, while the cap domain consists of a blue helical subdomain and a light blue maturation subdomain. (Figure generated using MOLSCRIPT (Kraulis (1991), *infra*)).

Figure 6A-B is a representation of the molecular surface of the PPCA dimer. The surface was calculated with GRASP (Nicholls, A., *et al., Proteins 11*:281-296 (1991)) and colored according to the electrostatic potential. Dark blue corresponds to positive potential > + 15.0 kT/e and dark red to a negative <-15.0 kT/e potential. Figure 6A: standard view, along the diad with the dimer oriented as in Figure 4. Figure 6B: side view of the dimer, ninety degrees rotated with respect to 6A.

Figure 7A-F presents a topological comparison of 6 members of the hydrolase fold family. The arrangement of structural elements in the central core domain (in green and yellow) of the different proteins is generally similar. The cap domains (in red) vary greatly. The following structures are shown starting from the top left hand corner (references and PDB entry codes are given in between brackets): Figure 7A shows the PPCA precursor cap domain that consists of two subdomains one α-helical and the other mainly β-sheet; Figure 7B shows CPW (3SC2, Liao *et al.* (1992) *infra*), cap domain helical; Figure 7C shows CPY (LYSC, Endrizzi *et al.* (1994), *infra*), cap domain helical; Figure 7D shows dehalogenase (2HAD, Franken *et al., J. EMBO 10*:1297-1302 (1991)), cap domain helical but quite different from the serine carboxypeptidases; Figure 7E shows lipase from *Pseudomonas glumae* (1TAH, Noble *et al., FEBS Lett. 331*:123-128 (1993)), cap domain mixed α-helical and β-strands; and Figure 7F shows acetylcholine esterase (1ACE, Sussman *et al., Science 253*: 872-879 (1991)), cap domain large and predominantly α-helical. The secondary structure assignments were generated with the computer program O, using structures provided and/or available from the Brookhaven Protein Data Bank. (This Figure was generated using MOLSCRIPT (Kraulis (1991), *infra*)).

Figure 8A-B shows the superposition of the C^α traces from the PPCA and CPW monomers, showing that the major differences between the two enzymes are localized in the cap domain. PPCA has a large 'maturation' subdomain and the 'helical subdomain' is rotated with respect to the CPW counterpart (Figure drawn with the O program (Jones (1991), *infra*)). Figure 8B shows the C^α traces from the PPCA and CPW dimers after the core domains from the subunits (shown on the right hand side of the two dimers) have been superimposed. Notice the remarkable difference in mutual orientation (of 15°) of the two subunits on the left hand side of the two dimers, which has been accentuated by an arrow. (Figure drawn with the O computer program (Jones (1991), *supra*)).

Figure 9 is a stereo view of the Ca trace of PPCA monomer 1 highlighting regions involved in the maturation event. Color scheme for the trace is as follows: core domain in light blue, helical subdomain in red, maturation subdomain in orange with the exception of the excision peptide (residues 285-298) which is shown in blue. Orange sphere mark the residues 272 and 277 marking the beginning and end of the blocking peptide. The catalytic triad Ser 150, His 429 and Asp 372 is shown as light blue spheres. Two cysteines Cys 253 and Cys 303 referred to in the discussion are colored green. (This Figure generated using MOLSCRIPT (Kraulis (1991), *infra*)).

Figure 10 is a close-up representation of the 'blocking' peptide (residues 272-277) bound in the active site, rendering the catalytic triad solvent inaccessible. Residues from the maturation subdomain are shown in orange, residues

from the helical domain in magenta and residues from the core domain in cyan. The excision peptide is shown in blue. Side chains are shown for residues making extensive contacts with the blocking peptide or if mentioned in the text. The catalytic triad is sh wn in white. (Figure drawn with O (Jones (1991), *infra*)).

Figure 11 is a representation of elements proposed to be involved in the activation mechanism of the precursor form of PPCA as discussed in the text. The C^{α}-trace of the core domain is shown in cyan, the helical subdomain in red, the maturation subdomain in orange, and the excision peptide is shown in blue. Relevant side chains are depicted and labeled. Rearrangement of the residues 254-302 limited by the disulfide Cys 253 and Cys 303 would free up the active site cleft. A charge cluster Arg 262, Glu 264, Arg 298 and Asp 300 occupies a strategic position within the maturation subdomain, possibly involved in pH dependent regulation of conformational changes. The solvent accessible surface was calculated and visualized with the atomic coordinates by BIOGRAF (BIOGRAF Construct Users Guide Version 3.2.1., June 1993).

Figure 12 is a schematic representation of the proposed activation of PPCA. The active site cleft is formed by the core domain (indicated as 'core' in the above scheme) and the helical subdomain (indicated as 'α'). The maturation subdomain (indicated as 'm') contains the residues that block the active site cleft rendering the precursor enzymatically inactive, shown in structure 1. In the acidic endosome/lysosome, the precursor undergoes activation. In activation pathway 2a, conformational rearrangements induced by low pH might render the excision peptide more accessible to proteases as a first step, followed by cleavage of the polypeptide chain removing the excision peptide. Alternatively, in pathway 2b, proteolytic cleavage of the excision peptide might form the trigger for the total rearrangement, removing the blocking peptide from the active site and thus generating the fully active enzyme as shown in structure 3.

Figure 13 shows the amino acid sequence of a human pPPCA. The underlined portion (residues 285-298) shows an excision peptide for conversion to the mature form, PPCA.

Figure 14 shows the amino acid sequence of a human PPCA.

Figure 15 shows a sequence alignment between pPPCA, CPW and CPY (top three sequences shown). Identical residues among all three sequences are boxed. Residue numbering is included for the pPPCA amino acid sequence. The alignment was made using the GCG program PILEUP (GCG version 8), then manually adjusted using 3D-structural knowledge from the superposition of the CPW (Liao *et al.*, 1992) and CPY (Endrizzi *et al.*, 1994) atomic coordinates. The alignment was later used to design a multi-Ala search probe for molecular replacement calculations shown in the fourth sequence shown as 'model'. The structure determination of pPPCA subsequently revealed that the protein can be divided in two domains: a 'core' domain (residues 1-182 and 303-452) and 'cap' domain (residues 183-302). The secondary structure elements for the PPCA precursor are depicted with shaded bars (for details on the assignment and nomenclature, see Rudenko *et al. Structure* 3:1249-1259 (1988)).

Figure 16 shows a schematic representation of a 'bootstrapping' cycle as described in Example 2.

Figure 17 is a representation of an initial molecular mask enlarged to accommodate missing area's in the model. The program MAMA (Kleywegt & Jones, 1994) was used to calculate the mask and mask editing options in O (Jones *et al.*, 1991) were used to extend the mask.

Figure 18 is a representation of an enlargement of the model during the bootstrapping procedure plotted as a function of the expansion step. The number of C^{α} atoms incorporated in the model per monomer is given (—▫—) as well as the number of correct side chains (--▫--). Note that after the first round of building in the molecular replacement map (expansion step 'mr'). 37 residues from the molecular replacement search probes had to be deleted from the model reducing the number of C^{α} atoms to 294. Subsequent cycles allowed for the model to be expanded by small increments.

Figure 19 is a representation of a comparison of the C^{α} trace from a monomer core model (shown in magenta) and the complete PPCA monomer (shown in yellow). The core model contained only 294 C^{α} atoms. The 452 residue PPCA monomer consists of a core domain and a cap domain. The helical subdomain and the maturation subdomain forming the cap domain have been shown in the figure above.

Figure 20A-D is a representation of the res lving power f the bootstrapping procedure showing three different stages in map quality. The atomic coordinates f the refined model are visualized with the electron density in Figures **20B. 20C** and **20D**. Figures **20A** and **20B** show the initial $2m|F_{obs}|-D|F_{calc}|$ SigmaA weighted map calculated using phases from the molecular replacement solution. The electron density is essentially uninterpretable. **Fig. 20C** shows twofold averaged $2|F_{obs}|-|F_{mw}|$electron density map calculated using inverted phases from cycle bmc6. The density for β-strand Mβ2 (residues 266-271) has become clearly visible. **Fig. 20D** shows unaveraged $2m|F_{obs}|-D|F_{calc}|$ SigmaA weighted map calculated using phases from the refined model. The quality of the density is very good. Density for the helix Mα1 (residues 287-293) which assumes a different conformation in the two monomers is now also apparent.

Figure 21 shows a Ramachandran plot calculated for one monomer from a refined model of a pPPCA. Both monomers in the asymmetric unit give essentially equivalent plots.

Figure 22 shows a schematic of a computer system for PPCA or pPPCA structure determination and/or rational drug design.

Figure 23.1-52 lists the atomic coordinates for the active site of a pPPCA dimer having the amino acid sequence presented as portions of at least one of 50-76, 144-155, 173-197, 226-253, 226-288, 294-310, 327-344, 338-350, 366-381 and 423-436 of (Figure 23.1-23.26) 452 amino acids (designated 1-452) of monomer 1, as well as corresponding portions of (Figure 23.26-23.52) 452 amino acids (designated 1001-1452) of monomer 2.

Detailed Description of the Preferred Embodiments

The present invention provides methods for expressing, purifying and crystallizing a protective protein/cathepsin A (PPCA) or a precursor protective protein/cathepsin A (pPPCA), where the crystals diffract x-rays with sufficiently high resolution to allow determination of the three-dimensional structure of the PPCA or pPPCA, or a portion or subdomain thereof. The three-dimensional structure (*e.g.*,as provided on computer readable media of the present invention) is useful for rational drug design of ligands of a PPCA or a pPPCA. Such ligands can be synthesized or recombinantly produced and are useful as diagnostic agents or drugs for diagnosing, treating, inhibiting or preventing at least one PPCA- or pPPCA-related pathology.

The determined structure is made using the PPCA or pPPCA amino acid sequences and/or atomic coordinate/x-ray diffraction data, which are analyzed to provide atomic model output data corresponding to the three-dimensional structure, *e.g.*, as provided on computer readable media. The computer analysis of the atomic coordinate/x-ray diffraction data and/or the amino acid sequence allows the calculation of the secondary, tertiary and/or quaternary structures; domains; and/or subdomains of the protein. These domains are combined and refined by additional calculations using suitable computer subroutines to determine the most probable or actual three-dimensional structure of the PPCA or pPPCA, including potential or actual active sites, binding sites or other structural or functional domains or subdomains of the protein.

Structure determination methods are also provided by the present invention for rational drug design (RDD) of PPCA or pPPCA ligands. Such drug design uses computer modeling programs that calculate different molecules expected to interact with the determined active sites, binding sites, or other structural or functional domains or subdomains of a PPCA or a pPPCA. These ligands can then be produced and screened for activity in modulating or binding to a PPCA or pPPCA, according to methods and compositions of the present invention.

The actual PPCA or pPPCA-ligand complexes can optionally be crystallized and analyzed using x-ray diffraction techniques. The diffraction patterns obtained are similarly used to calculate the three-dimensional interaction of the ligand and the PPCA or pPPCA, to confirm that the ligand binds to, or changes the conformation of, particular domain(s) or subdomain(s) of the PPCA or pPPCA. Such screening methods are selected from assays for at least one biological activity of a PPCA or a pPPCA. The resulting ligands, provided by methods of the present invention, modulate or bind at least one PPCA or pPPCA and are useful for diagnosing, treating or preventing PPCA- or pPPCA-related pathologies in animals, such as humans. Ligands of a particular PPCA or pPPCA can similarly modulate other PPCAs or pPPCAs from other sources, such as other eukaryotes.

A PPCA or pPPCA is also provided as a crystallized protein suitable for x-ray diffraction analysis. The x-ray diffraction patterns obtained by the x-ray analysis are of moderate, to moderately high, to high resolution, *e.g.*, 30-10, 10-3.5 or 1.5-3.5 Å, respectively, with the higher resolutions included. These diffraction patterns are suitable and useful for three-dimensional structure determination of a PPCA or a pPPCA, domain or subdomain thereof.

The determination of the three-dimensional structure of a PPCA or pPPCA has a broad-based utility. Significant sequence identity and conservation of important structural elements are expected to exist among different PPCAs or pPPCAs. Therefore, the three-dimensional structure from one or few PPCAs or pPPCAs can be used to identify ligands that have diagnostic or therapeutic value for at least one PPCA- or pPPCA-related pathology that may involve PPCAs or pPPCAs having different amino acid sequences.

Determination of Protein Structures

Different techniques give different and complementary information about protein structure. The primary structure is obtained by biochemical methods, either by direct determination of the amino acid sequence from the protein, or from the nucleotide sequence of the corresponding gene or cDNA. The quaternary structure of large proteins or aggregates can also be determined by electron microscopy. To obtain the secondary and tertiary structure, which requires detailed information about the arrangement of atoms within a protein, x-ray crystallography is preferred. *See, e.g.*, Blundell, *infra*; Oxender, *infra*; McPherson, *infra*; Wyckoff, *infra*.

The first prerequisite for solving the three-dimensional structure of a protein by x-ray crystallography is a well-ordered crystal that will diffract x-rays strongly. The crystallographic method directs a beam of x-rays onto a regular, repeating array of many identical molecules so that the x-rays are diffracted from it in a pattern from which the structure of an individual molecule can be retrieved. Well-ordered crystals of globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and crystals thereof contain large holes or channels that are formed between the individual molecules. These channels, which usually occupy more than half the volume of the crystal, are filled with disordered solvent molecules. The protein molecules are in contact with each other at only a few small regions. This is one reason why structures of proteins determined by x-ray crystallography are generally the same as those for the proteins in solution.

The formation of crystals is dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions or ligands to the protein. Many routine crystallization experiments may be needed to screen all these parameters for the few combinations that might give crystal suitable for x-ray diffraction analysis. Crystallization robots can automate and speed up the work of reproducibly setting up large numbers of crystallization experiments.

A pure and homogeneous protein sample is important for successful crystallization. Proteins obtained from cloned genes in efficient expression vectors can be purified quickly to homogeneity in large quantities in a few purification steps. A protein to be crystallized is preferably at least 93-99% pure according to standard criteria of homogeneity. Crystals form when molecules are precipitated very slowly from supersaturated solutions. The most frequently used procedure for making protein crystals is the hanging-drop method, in which a drop of protein solution is brought very gradually to supersaturation by loss of water from the droplet to the larger reservoir that contains salt or polyethylene glycol solution.

Different crystal forms can be more or less well-ordered and hence give diffraction patterns of different quality. As a general rule, the more closely the protein molecules pack, and consequently the less water the crystals contain, the better is the diffraction pattern because the molecules are better ordered in the crystal.

X-rays are electromagnetic radiation at short wavelengths, emitted when electrons jump from a higher to a lower energy state. In conventional sources in the laboratory, x-rays are produced by high-voltage tubes in which a metal plate, the anode, is bombarded with accelerating electrons and thereby caused to emit x-rays of a specific wavelength, so-called monochromatic x-rays. The high voltage rapidly heats up the metal plate, which therefore has

to be cooled. Efficient cooling is achieved by so-called rotating anode x-ray generators, where the metal plate revolves during the experiment so that different parts are heated up.

More powerful x-ray beams can be produced in synchrotron storage rings where electrons (or positrons) travel close to the speed of light. These particles emit very strong radiation at all wavelengths from short gamma rays to visible light. When used as an x-ray source, only radiation within a window of suitable wavelengths is channeled from the storage ring. Polychromatic x-ray beams are produced by having a broad window that allows through x-ray radiation with wavelengths of 0.2 - 3.5 Å.

In diffraction experiments a narrow and parallel beam of x-rays is taken out from the x-ray source and directed onto the crystal to produce diffracted beams. The incident primary beam causes damage to both protein and solvent molecules. The crystal is, therefore, usually cooled to prolong its lifetime (*e.g.*, -220 to -50°C). The primary beam must strike the crystal from many different directions to produce all possible diffraction spots, and so the crystal is rotated in the beam during the experiment.

The diffracted spots are recorded either on a film, the classical method, or by an electronic detector. The exposed film has to be measured and digitized by a scanning device, whereas electronic detectors feed the signals they detect directly in a digitized form into a computer. Electronic area detectors (an electronic film) significantly reduce the time required to collect and measure diffraction data.

When the primary beam from an x-ray source strikes the crystal, some of the x-rays interact with the electrons on each atom and cause them to oscillate. The oscillating electrons serve as a new source of x-rays, which are emitted in almost all directions, referred to as scattering. When atoms (and hence their electrons) are arranged in a regular three-dimensional array, as in a crystal, the x-rays emitted from the oscillating electrons interfere with one another. In most cases, these x-rays, colliding from different directions, cancel each other out; those from certain directions, however, will add together to produce diffracted beams of radiation that can be recorded as a pattern on a photographic plate or detector.

The diffraction pattern obtained in an x-ray experiment is related to the crystal that caused the diffraction. X-rays that are reflected from adjacent planes travel different distances, and diffraction only occurs when the difference in distance is equal to the wavelength of the x-ray beam. This distance is dependent on the reflection angle, which is equal to the angle between the primary beam and the planes.

The relationship between the reflection angle (θ), the distance between the planes (d), and the wavelength (λ) is given by Bragg's law: $2d \sin \theta = \lambda$. This relation can be used to determine the size of the unit cell in the crystal. Briefly, the position on the film of the diffraction data relates each spot to a specific set of planes through the crystal. By using Bragg's law, these positions can be used to determine the size of the unit cell.

Each atom in a crystal scatters x-rays in all directions, and only those that positively interfere with one another, according to Bragg's law, give rise to diffracted beams that can be recorded as a distinct diffraction spot above background. Each diffraction spot is the result of interference of all x-rays with the same diffraction angle emerging from all atoms. For example, for the protein crystal of myoglobin, each of the about 20,000 diffracted beams that have been measured contain scattered x-rays from each of the around 1500 atoms in the molecule. To extract information about individual atoms from such a system requires considerable computation. The mathematical tool that is used to handle such problems is called the Fourier transform.

Each diffracted beam, which is recorded as a spot on the film, is defined by three properties: the amplitude, which we can measure from the intensity of the spot; the wavelength, which is set by the x-ray source; and the phase, which is lost in x-ray experiments. All three properties are needed for all of the diffracted beams, in order to determine the position of the atoms giving rise to the diffracted beams.

For larger molecules, protein crystallographers have determined the phases in many cases using a method called multiple isomorphous replacement (MIR) (including heavy metal scattering), which requires the introduction of new x-ray scatterers into the unit cell of the crystal. These additions are usually heavy atoms (so that they make a significant

contribution to the diffraction pattern), such that there should not be too many of them (so that their positions can be located); and they should not change the structure of the molecule or of the crystal cell, *i.e.*, the crystals should be isomorphous. Isomorphous replacement is usually done by diffusing different heavy-metal complexes into the channels of the preformed protein crystals. The protein molecules expose side chains (such as SH groups) into these solvent channels that are able to bind heavy metals. It is also possible to replace endogenous light metals in metalloproteins with heavier ones, *e.g.*, zinc by mercury, or calcium by samarium.

Since such heavy metals contain many more electrons than the light atoms (H, N, C, O, and S) of the protein, they scatter x-rays more strongly. All diffracted beams would therefore increase in intensity after heavy-metal substitution if all interference were positive. In fact, however, some interference is negative; consequently, following heavy-metal substitution, some spots measurably increase in intensity, others decrease, and many show no detectable difference.

Phase differences between diffracted spots can be determined from intensity changes following heavy-metal substitution. First, the intensity differences are used to deduce the positions of the heavy atoms in the crystal unit cell. Fourier summations of these intensity differences give maps of the vectors between the heavy atoms, the so-called Patterson maps. From these vector maps the atomic arrangement of the heavy atoms is deduced. From the positions of the heavy metals in the unit cell, one can calculate the amplitudes and phases of their contribution to the diffracted beams of protein crystals containing heavy metals.

This knowledge is then used to find the phase of the contribution from the protein in the absence of the heavy-metal atoms. As both the phase and amplitude of the heavy metals and the amplitude of the protein alone is known, as well as the amplitude of the protein plus heavy metals (*i.e.*, protein heavy-metal complex), one phase and three amplitudes are known. From this, the interference of the x-rays scattered by the heavy metals and protein can be calculated to see if it is constructive or destructive. The extent of positive or negative interference, with knowledge of the phase of the heavy metal, give an estimate of the phase of the protein. Because two different phase angles are determined and are equally good solutions, a second heavy-metal complex can be used which also gives two possible phase angles. Only one of these will have the same value as one of the two previous phase angles; it therefore represents the correct phase angle. In practice, more than two different heavy-metal complexes are usually made in order to give a reasonably good phase determination for all reflections. Each individual phase estimate contains experimental errors arising from errors in the measured amplitudes. Furthermore, for many reflections, the intensity differences are too small to measure after one particular isomorphous replacement, and others can be tried.

The amplitudes and the phases of the diffraction data from the protein crystals are used to calculate an electron-density map of the repeating unit of the crystal. This map then has to be interpreted as a polypeptide chain with a particular amino acid sequence. The interpretation of the electron-density map is made more complex by several limitations of the data. First of all, the map itself contains errors, mainly due to errors in the phase angles. In addition, the quality of the map depends on the resolution of the diffraction data, which in turn depends on how well-ordered the crystals are. This directly influences the image that can be produced. The resolution is measured in Å units; the smaller this number is, the higher the resolution and therefore the greater the amount of detail that can be seen.

Building the initial model is a trial-and-error process. First, one has to decide how the polypeptide chain weaves its way through the electron-density map. The resulting chain trace constitutes a hypothesis, by which one tries to match the density of the side chains to the known sequence of the polypeptide. When a reasonable chain trace has finally been obtained, an initial model is built to give the best fit of the atoms to the electron density. Computer graphics are used both for chain tracing and for model building to present the data and manipulated the models.

The initial model will contain some errors. Provided the protein crystals diffract to high enough resolution (*e.g.*, better than 3.5 Å), most or substantially all of the errors can be removed by crystallographic refinement of the model using computer algorithms. In this process, the model is changed to minimize the difference between the experimentally observed diffraction amplitudes and those calculated for a hypothetical crystal containing the model (instead of the real

molecule). This difference is expressed as an R factor (residual disagreement) which is 0.0 for exact agreement and about 0.59 for total disagreement.

In general, the R factor is preferably between 0.15 and 0.35 (such as less than about 0.24-0.28) for a well-determined protein structure. The residual difference is a consequence of errors and imperfections in the data. These derive from various sources, including slight variations in the conformation of the protein molecules, as well as inaccurate corrections both for the presence of solvent and for differences in the orientation of the microcrystals from which the crystal is built. This means that the final model represents an average of molecules that are slightly different both in conformation and orientation.

In refined structures at high resolution, there are usually no major errors in the orientation of individual residues, and the estimated errors in atomic positions are usually around 0.1-0.2 Å, provided the amino acid sequence is known. Hydrogen bonds, both within the protein and to bound ligands, can be identified with a high degree of confidence.

Most x-ray structures are determined to a resolution between 1.7 Å and 3.5 Å. Electron-density maps with this resolution range are preferably interpreted by fitting the known amino acid sequences into regions of electron density in which individual atoms are not resolved.

An amino acid sequence is preferred for accurate x-ray structure determination. Thus, recombinant DNA techniques have had a double impact on x-ray structural work. When a protein is cloned and overexpressed for structural studies, the amino acid sequence, necessary for the x-ray work, is also quickly obtained via the nucleotide sequence. Recombinant DNA techniques give us not only abundant supplies of rare proteins, but also their amino acid sequence as a bonus. *See, e.g.*, Blundell, *infra*; Oxender, *infra*; McPherson, *infra*; Wyckoff, *infra*.

Isolated PPCA and pPPCA Polypeptides

A PPCA or pPPCA polypeptide can refer to any subset of a PPCA or pPPCA as a domain, subdomain, fragment, consensus sequence or repeating unit thereof. A PPCA or pPPCA polypeptide of the present invention can be prepared by, *e.g.*,:

(a) recombinant DNA methods;

(b) proteolytic digestion of the intact molecule or a domain, subdomain or fragment thereof;

(c) chemical peptide synthesis methods well-known in the art; and/or

(d) by any other method capable of producing a PPCA or pPPCA polypeptide and having a conformation similar to a structural or functional subdomain of a PPCA or a pPPCA.

A biological activity of PPCA or pPPCA can be screened according to known screening assays. The minimum peptide sequence to have activity is based on the smallest unit containing or comprising a particular domain, subdomain, fragment, region, consensus sequence, or repeating unit thereof, having at least one biological activity of a PPCA or pPPCA, such as protecting activity, inhibiting activity or enzyme activity. Non-limiting examples of such activities are: protecting activity for β-galactosidase or neuraminidase (NA); modulating activity (inhibition, stimulation or activation) as an for endothelin I (serine carboxypeptidase) or cathepsin A and peptide hydrolyzing activity (*e.g.*, substance P and substance P-free acid; oxytocin and oxytocin-free acid; neurokinin A; angiotensin I; and bradykinin.

According to the present invention, a PPCA or pPPCA includes an association of two or more polypeptide subdomains, such as at least one 4 amino acid portion of a core or cap domain of a PPCA or pPPCA. This can include 1-14 subdomains of the cap domain and/or 1-44 subdomains of the core domain (as monomers or dimers), or any range, value or combination thereof. Preferably 1-4 sets of each of at least one core or cap domains or subdomains are included.

The structure of a monomer or domain of at least one PPCA includes at least one subdomain of a PPCA of a pPPCA of the present invention can include one or more of the following subdomains, as described herein. Generally a PPCA or pPPCA consists of a dimer of a core domain and a cap domain having the following subdomains having the specified residues, e.g., as presented in Figure 13 (pPPCA) or Figure 14 (PPCA)::

Core domain subdomains: Cβ1, 21-27; Cβ2, 32-39; Cβ3, 50-54; Cα1, 63-67; Cβ4, 73-75; Cβ5, 82-84; Cβ6, 94-98; Cα2, 118-135; Cβ7, 144-149; Cα3, 152-163; Cβ8, 171-177; Cα4, 307-313; Cα5, 316-321; Cα6, 336-341; Cα7, 350-359; Cβ9, 363-369; Cα8, 377-386; Cβ10, 391-401; Cβ11, 407-416; Cβ12, 419-424; Cα9, 431-434; Cα10, 436-447; and

Cap domain subdomains: Hα1, 183-196; Hα2, 202-212; Hα 3, 226-240; Mβ1, 261-264; Mβ2, 267-270; Mα1, 290-293; Mβ3, 296-299. Note that for monomer 2 the secondary structure assignments in the cap domain are slightly different than in monomer 1.

A PPCA or pPPCA polypeptide of the invention can have at least 80% homology, such as 80-100% overall homology or identity, with one or more corresponding PPCA or pPPCA subdomains or fragments as described herein, such as a 4-542 amino acid fragment or portion of the amino acid sequence of Figures 13, 14 or 15. As would be understood by one of ordinary skill in the art, the above configurations of subdomains are provided as part of a PPCA or pPPCA polypeptide of the invention, when expressed in a suitable host cell, or otherwise synthesized, to provide at least one structural or functional feature of a native PPCA or pPPCA, such as at least one PPCA-related biological activity. Such activities can be assayed using a suitable assay, to establish at least one PPCA biological activity of one or more PPCAs or pPPCAs of the invention. A PPCA or pPPCA polypeptide of the invention is not naturally occurring or is naturally occurring but is in a purified or isolated form which does not occur in nature. Examples of suitable PPCA activity assay include, *e.g.*, cathepsin A activity (Galjart *et al., J. Biol. Chem. 266*:14754-14762 (1991); Endothelin I deamidase activity (Jackman, *et al., J. Biol. Chem. 267*:2872-2875(1992); and tachykinin deamidase activity (Jackman, *et al., J. Biol. Chem. 265*:11265-11272 (1990)).

Percent homology or identity can be determined, for example, by comparing sequence information using the GAP computer program, version 6.0, available from the University of Wisconsin Genetics Computer Group (UWGCG). The GAP program utilizes the alignment method of Needleman and Wunsch (*J. Mol. Biol.* 48:443 (1970), as revised by Smith and Waterman (*Adv. Appl. Math.* 2:482 (1981). Briefly, the GAP program defines similarity as the number of aligned symbols (i.e., nucleotides or amino acids) which are similar, divided by the total number of symbols in the shorter of the two sequences. The preferred default parameters for the GAP program include: (1) a unitary comparison matrix (containing a value of 1 for identities and 0 for non-identities) and the weighted comparison matrix of Gribskov and Burgess, *Nucl. Acids Res.* 14:6745 (1986), as described by Schwartz and Dayhoff, eds., *ATLAS OF PROTEIN SEQUENCE AND STRUCTURE*, National Biomedical Research Foundation, pp. 353-358 (1979); (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

Thus, one of ordinary skill in the art, given the teachings and guidance presented in the present specification, will know how to add, delete or substitute other amino acid residues in other positions of a PPCA or pPPCA to obtain substituted, deletional or additional variants thereof.

Non-limiting examples of substitutions of a PPCA or pPPCA domains or polypeptide of the invention are those in which at least one amino acid residue in the protein molecule has been removed and a different residue added in its place according to the following Table 2. The types of substitutions which can be made in the protein or peptide molecule of the invention can be based on analysis of the frequencies of amino acid changes between a homologous protein of different species, such those presented in Figure 15. Based on such an analysis, alternative substitutions are defined herein as exchanges within one of the following five groups:

1. Small aliphatic, nonpolar or slightly polar residues: Ala, Ser, Thr (Pro, Gly);
2. Polar, negatively charged residues and their amides: Asp, Asn, Glu, Gln;
3. Polar, positively charged residues:
   His, Arg, Lys;
4. Large aliphatic, nonpolar residues:
   Met, Leu, Ile, Val (Cys); and
5. Large aromatic residues: Phe, Tyr, Trp.

Most deletions and additions, and substitutions according to the invention are those which do not produce radical changes in the characteristics of the protein or peptide molecule. "Characteristics" is defined in a non-inclusive

manner to define both changes in secondary structure, e.g. α-helix or β-sheet, as well as changes in physiological activity, *e.g.*. in biological activity assays. However, when the exact effect of the substitution, deletion, or addition is to be confirmed, one skilled in the art will appreciate that the effect of at least one substitution, addition or deletion will be evaluated by at least one PPCA or pPPCA screening assay, such as, but not limited to, immunoassays or bioassays, to confirm at least one PPCA or pPPCA biological activity.

Surprisingly, a PPCA and/or a pPPCA is now discovered to have serine carboxypeptidase activity and corresponding structural features, although having only about 30% sequence identity to wheat and yeast serine carboxypeptidases. These carboxypeptidases are members of the hydrolase fold family (Liao *et al., Biochemistry 31*:9796-9812 (1992); Endrizzi *et al.,Biochemistry 33*:11106-11120 (1994); Ollis *et al., Protein Eng. 5*:197-211 (1992)). The serine carboxypeptidases have peptidase activity at acidic pH (pH 4.5-5.5) as well as deamidase and esterase activities at pH 7 (reviewed in Breddam *et al. Carlsberg Res. Commun. 51*:83-128 (1986); Rawlings & Barrett, *Methods in Enzymology. 244*:19-61 (1994)). Mutagenesis studies and enzymatic assays have revealed that only the mature form of PPCA possesses a serine carboxypeptidase activity, which is similar to that of lysosomal cathepsin A, and has a preference for hydrophobic substrates such as the dipeptide Phe-Ala (Galjart *et al., J. Biol. Chem. 266*:14754-14762 (1991)). On the basis of sequence alignments with members of the serine carboxypeptidase family, mutagenesis studies and the structure determination of pPPCA, the catalytic triad in PPCA has now been determined to be formed by the residues Ser 150, His 429 and Asp 372

PPCA and pPPCA Expression for Isolation and Purification

A nucleic acid sequence encoding a PPCA or a pPPCA (Galjart *et al., Cell. 54*:755-764 (1988)) can be recombined with vector DNA in accordance with conventional techniques, including blunt-ended or staggered-ended termini for ligation, restriction enzyme digestion to provide appropriate termini, filling in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and ligation with appropriate ligases. Techniques for such manipulations are disclosed, *e.g.*, in Sambrook *et al., Molecular Cloning: A Laboratory Manual*, Second edition, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989); and Ausubel *et al.,Current Protocols in Molecular Biology*, Wiley Interscience, N.Y., (1988-1995) and are well known in the art.

A nucleic acid molecule, such as DNA, is said to be "capable of expressing" a polypeptide if it contains nucleotide sequences which contain transcriptional and translational regulatory information and such sequences are "operably linked" to nucleotide sequences which encode the polypeptide. An operable linkage is a linkage in which the regulatory DNA sequences and the DNA sequence sought to be expressed are connected in such a way as to permit gene expression as a PPCA , pPPCA or fragment thereof, in recoverable amounts. The precise nature of the regulatory regions needed for gene expression can vary from organism to organism, as is well known in the analogous art. See, *e.g.*, Sambrook, *infra* and Ausubel, *infra*.

The invention accordingly encompasses the expression of a PPCA or a pPPCA, in either prokaryotic or eukaryotic cells, although eukaryotic expression is preferred. Preferred hosts are bacterial or eukaryotic hosts including bacteria, yeast, insects, fungi, bird and mammalian cells either *in vivo*, or *in situ*, or host cells of mammalian, insect, bird or yeast origin. It is preferred that the mammalian cell or tissue is of human, primate, hamster, rabbit, rodent, cow, pig, sheep, horse, goat, dog or cat origin, but any other mammalian cell can be used.

Eukaryotic hosts can include yeast, insects, fungi, and mammalian cells either *in vivo*, or in tissue culture. Preferred eukaryotic hosts can also include, but are not limited to insect cells, mammalian cells either *in vivo*, or in tissue culture. Preferred mammalian cells include *Xenopus* oocytes, HeLa cells, cells of fibroblast origin such as VERO or CHO-K1, or cells of lymphoid origin and their derivatives.

Mammalian cells provide post-translational modifications to protein molecules including correct folding or glycosylation at correct sites. Mammalian cells which can be useful as hosts include cells of fibroblast origin such as, but not limited to, NIH 3T3, VERO or CHO, or cells of lymphoid origin, such as, but not limited to, the hybridoma SP2/O-Ag14 or the murine myeloma P3-X63Ag8, hamster cell lines (e.g., CHO-K1 and progenitors, e.g., CHO-

DUXB11) and their derivatives. One preferred type of mammalian cells are cells which are intended to replace the function of the genetically deficient cells *in vivo*. Neuronally derived cells are preferred for gene therapy of disorders of the nervous system. For a mammalian cell host, many possible vect r systems are available for the expression of at least one PPCA or pPPCA. A wide variety of transcriptional and translational regulatory sequences can be employed, depending upon the nature of the host. The transcriptional and translational regulatory signals can be derived from viral sources, such as, but not limited to, adenovirus, bovine papilloma virus, Simian virus, or the like, where the regulatory signals are associated with a particular gene which has a high level of expression. Alternatively, promoters from mammalian expression products, such as, but not limited to, actin, collagen, myosin, protein production.

When live insects are to be used, silk moth caterpillars and baculoviral vectors are presently preferred hosts for large scale PPCA or pPPCA production according to the invention. Production of PPCA or pPPCA in insects can be achieved, for example, by infecting the insect host with a baculovirus engineered to express transmembrane polypeptide by methods known to those skilled in the related arts. See Ausubel *infra*, §§16.8-16.11.

In a preferred embodiment, the introduced nucleotide sequence will be incorporated into a plasmid or viral vector capable of autonomous replication in the recipient host. Any of a wide variety of vectors can be employed for this purpose. See, *e.g.*, Ausubel *et al.*, *infra*, §§ 1.5, 1.10, 7.1, 7.3, 8.1, 9.6, 9.7, 13.4, 16.2, 16.6, and 16.8-16.11. Factors of importance in selecting a particular plasmid or viral vector include: the ease with which recipient cells that contain the vector can be recognized and selected from those recipient cells which do not contain the vector; the number of copies of the vector which are desired in a particular host; and whether it is desirable to be able to "shuttle" the vector between host cells of different species.

Different host cells have characteristic and specific mechanisms for the translational and post-translational processing and modification (*e.g.*, glycosylation, cleavage) of proteins. Appropriate cell lines or host systems can be chosen to ensure the desired modification and processing of the foreign protein expressed. For example, expression in a bacterial system can be used to produce an unglycosylated core protein product. Expression in yeast will produce a glycosylated product. Expression in mammalian cells can be used to ensure "native" glycosylation of the heterologous PPCA or pPPCA. Furthermore, different vector/host expression systems can effect processing reactions such as proteolytic cleavages to different extents.

As discussed above, expression of PPCA or pPPCA in eukaryotic hosts requires the use of eukaryotic regulatory regions. Such regions will, in general, include a promoter region sufficient to direct the initiation of RNA synthesis. *See, e.g.*, Ausubel, *infra*; Sambrook, *infra*.

Once the vector or nucleic acid molecule containing the construct(s) has been prepared for expression, the DNA construct(s) can be introduced into an appropriate host cell by any of a variety of suitable means, i.e., transformation, transfection, conjugation, protoplast fusion, electroporation, particle gun technology, calcium phosphate-precipitation, direct microinjection, and the like. After the introduction of the vector, recipient cells are grown in a selective medium, which selects for the growth of vector-containing cells. Expression of the cloned gene molecule(s) results in the production of a PPCA or pPPCA. This can take place in the transformed cells as such, or following the induction of these cells to differentiate (for example, by administration of bromodeoxyuracil to neuroblastoma cells or the like).

A PPCA or pPPCA, or fragments thereof, of this invention can be obtained by expression from recombinant DNA according to known methods. Alternatively, a PPCA or pPPCA can be purified from biological material. A PPCA or a pPPCA can be purified from different mammalian tissues (*e.g.*, human placenta, rat liver, mouse liver, pig kidney, bovine testes, bovine liver, and the like) of various genus and species.

The PPCA or pPPCA can be isolated and purified in accordance with conventional method steps, such as extraction, precipitation, chromatography, affinity chromatography, electrophoresis, or the like. For example, cells expressing at least one PPCA or pPPCA in suitable levels can be collected by centrifugation, or with suitable buffers, lysed, and the protein isolated by column chromatography, for example, on DEAE-cellulose, phosphocellulose, polyribocytidylic acid-agarose, hydroxyapatite or by electrophoresis or immunoprecipitation. Alternatively, a pPPCA

or PPCA can be isolated by the use of antibodies, such as, but not limited to, a PPCA- or pPPCA-specific antibody. Such antibodies can be obtained by known method steps (*see, e.g.*, Harlow and Lane *ANTIBODIES: A LABORATORY MANUAL* Cold Spring Harbor Laboratory (1988); Colligan *et al.*, eds., *Current Protocols in Immunology*, Greene Publishing Assoc. and Wiley Interscience, N.Y., (1992, 1993), the contents of which references are entirely incorporated herein by reference).

A PPCA or a pPPCA can be purified from different mammalian tissues (*e.g.*, human placenta, rat liver, mouse liver, pig kidney, bovine testes, bovine liver, and the like) of various genus and species, using known techniques such as gel filtration, phase separation and affinity chromatography, *e.g.*,using polyclonal or monoclonal antibodies specific for a PPCA or pPPCA, according to known methods. *See., e.g.*, Oxender *et al., Protein Engineering*, Liss, New York (1986).

Overview of PPCA or pPPCA Purification and Crystallization Methods

In general, a PPCA or pPPCA is isolated in soluble form in sufficient purity and concentration (*e.g.*, a monomer or dimer) for crystallization. The PPCA or pPPCA is then isolated and assayed for biological activity (*e.g.*, cathepsin A) and for lack of aggregation (which interferes with crystallization). The purified PPCA or pPPCA preferably runs as a single band for each monomer under reducing or nonreducing polyacrylamide gel electrophoresis (PAGE) (nonreducing is used to evaluate the presence of cysteine bridges).

The purified PPCA or pPPCA is preferably crystallized under varying conditions of at least one of the following: pH, buffer type, buffer concentration, salt type, polymer type, polymer concentration, other precipitating ligands and concentration of purified PPCA or pPPCA. See, *e.g.*, known methods (Blundell *et al., Protein Crystallography*, Academic Press, London (1976); Oxender, *infra*; McPherson, *The Preparation and Analysis of Protein Crystals*, Wiley Interscience, N.Y. (1982)) or methods provided in a commercial kit, such as CRYSTAL SCREEN (Hampton Research, Riverside, CA). The crystallized PPCA protein can optionally be tested for at least one PPCA activity and differently sized and shaped crystals are further tested for suitability for x-ray diffraction. Generally, larger crystals provide better crystallographic data than smaller crystals, and thicker crystals provide better crystallographic data than thinner crystals. *See, e.g.*, Blundell, *infra*; Oxender, *infra*; McPherson, *infra*; Wyckoff *et al., Diffraction Methods for Biological Macromolecules*Vols. 114-115, *Methods in Enzymology*, Academic Press, Orlando, FL (1985).

Protein Crystallization Methods

The hanging drop method is preferably used to crystallize the purified protein. *See, e.g.*, Blundell, *infra*; Oxender, *infra*; McPherson, *infra*; Wyckoff, *infra*; Taylor *et al., J. Mol. Biol. 226*:1287-1290 (1992); Takimoto *et al.* (1992), *infra*; CRYSTAL SCREEN, Hampton Research.

A mixture of the purified protein and precipitant can include the following:

- pH (*e.g.*, 7-9);
- buffer type (*e.g.*, tromethamine (TRIZMA), sodium azide (NaN_3), phosphate, sodium, or cacodylate acetates, imidazole, Tris HCl, sodium hepes);
- buffer concentration (*e.g.*, 1-100 mM);
- salt type (*e.g.*, sodium azide, calcium chloride, sodium citrate, magnesium chloride, ammonium acetate, ammonium sulfate, potassium phosphate, magnesium acetate, zinc acetate; calcium acetate)
- polymer type and concentration: (*e.g.*, polyethylene glycol (PEG) 1-50%, type 400-10,000);
- other additives (salts: potassium, sodium, tartrate, ammonium sulfate, sodium acetate, lithium sulfate, sodium formate, sodium citrate, magnesium formate, sodium phosphate, potassium phosphate; organics: 2-propanol; non-volatile: 2-methyl-2,4-pentanediol); β-octyl glucoside and
- concentration of purified PPCA or pPPCA (*e.g.*, 1.0-100 mg/ml).

See, e.g., CRYSTAL SCREEN, Hampton Research.

A non-limiting example of such crystallization conditions is the following:

- purified PPCA or pPPCA protein (*e.g.*, 5 mg/ml);

- (2) solutions in serial mixtures
  - (1) 40-80 mM TRIZMA, 0.05-2.0 mM NaN_3;
  - (2) 2-30% Polyethylene glycol (PEG) 8000 buffered with 40-80 mM TRIZMA and 0.05-2.0 mM NaN_3
- 0.05-0.5% β-octyl glucoside;
- at an overall pH of about 8.0-8.3.

The above mixtures are used and screened by varying at least one of pH, buffer type, buffer concentration, precipitating salt type or additive or their concentrations, PEG type, PEG concentration, and protein concentration. Crystals ranging in size from 0.1-0.9 mm are formed in 1 -14 days. These crystals diffract x-rays to at least 10 Å resolution, such as 0.15-10.0 Å, or any range of value therein, such as 1.5, 1.6, 1.7. 1.8, 1.9, 2.0, 2.1, 2.2. 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4 or 3.5, with 3.5 Å or higher being preferred for the highest resolution. In addition to diffraction patterns having this highest resolution, lower resolution, such as 25-3.5 Å can also be used. *See, e.g.*, Blundell, *infra*; Oxender, *infra*; McPherson, *infra*; Wyckoff, *infra*;

Protein Crystals

Crystals appear after 1-14 days and continue to grow on subsequent days. Some of the crystals can be optionally removed, washed, and assayed for biological activity (*e.g.*, PPCA), which activity is preferred for using in further characterizations. Other washed crystals are preferably run on a gel and stained, and those that migrate in the same position as the purified PPCA or pPPCA are preferably used. From two to one hundred crystals are observed in one drop and crystal forms can occur, such as, but not limited to, orthorombic, bipyramidal, rhomboid, and cubic. Initial x-ray analyses indicate that such crystals diffract at moderately high to high resolution. When fewer crystals are produced in a drop, they can be much larger size, *e.g.*, 0.4-0.9 mm. *See, e.g.*, Blundell, *infra*; Oxender, *infra*; McPherson, *infra*; Wyckoff, *infra*;

PPCA and pPPCA X-ray Crystallography Methods

The crystals so produced for a PPCA or pPPCA are x-ray analyzed using a suitable x-ray source. Diffraction patterns are obtained. Crystals are preferably stable for at least 10 hrs in the x-ray beam . Frozen crystals (*e.g.*, -220 to -50°C) are optionally used for longer x-ray exposures (*e.g.*, 5-72 hrs), the crystals being relatively more stable to the x-rays in the frozen state. To collect the maximum number of useful reflections, multiple frames are optionally collected as the crystal is rotated in the x-ray beam, *e.g.*, for 5-72 hrs. Larger crystals (>0.2 mm) are preferred, to increase the resolution of the x-ray diffraction patterns obtained. Crystals are preferably analyzed using a synchrotron high energy x-ray source. Using frozen crystals, x-ray diffraction data is collected on crystals that diffract to at least a relatively high resolution of 10-1.5 Å, with lower resolutions also useful, such as 25-10Å, sufficient to solve the three-dimensional structure of a PPCA or pPPCA in considerable detail, as presented herein.

Passing an x-ray beam through a crystal produces a diffraction pattern as a result of the x-rays interacting and being scattered by the contents of the crystal. The diffraction pattern can be visualized using, *e.g.*, an image plate or film, resulting in an image with spots corresponding to the diffracted x-rays. The positions of the spots in the diffraction pattern are used to determine parameters intrinsic to the crystal (such as unicell parameters) and to gain information on the packing of the molecules in the crystal. The intensity of the spots contains the Fourier transformation of the molecules in the crystal, *i.e.*, information on each atom in the crystal and hence of the crystallized molecule.

After data collection of diffraction patterns, the data is processed. This includes measuring the spots on each diffraction pattern in terms of position and intensity. This information is processed (*i.e.*, mathematical operations are performed on the data (such as scaling, merging and converting the data from intensity of diffracted beams to amplitudes)) to yield a set of data which is in a form as can be used for the further structure determination of the molecule crystallized. The amplitudes of the diffracted x-rays are then combined with calculated phases to produce an electron density map of the contents of the crystal. In this electron density map, the structure of the molecules (as

present in the crystal) is built. The phases can be determined with various known techniques. one being molecular replacement.

For the molecular replacement technique one takes a known three dimensi nal structure thought to share structural homology with the structure to be determined, to generate after calculations a first set of initial phases. These phases are then combined with the diffraction information of the molecule for which you want to solve the structure of. The result is an electron density map of the molecules in the crystal from which the diffraction patterns originate.

The phases can be further optimized using a technique called density modification, which allows electron density maps of better quality to be produced facilitating interpretation and model building therein. The atomic model is then refined by allowing the atoms in the model to move in order to match the diffraction data as well as possible while continuing to satisfy stereochemical constraints (sensible bond lengths, bond angles and the like). *See, e.g.*, Blundell, *infra*; Oxender, *infra*; McPherson, *infra*; Wyckoff, *infra*;

Computer Related Embodiments

An amino acid sequence of a PPCA or pPPCA and/or atomic coordinate/x-ray diffraction data, useful for computer structure determination of a PPCA, pPPCA or a portion thereof, can be "provided" in a variety of mediums to facilitate use thereof. As used herein, provided refers to a manufacture, which contains a PPCA or pPPCA amino acid sequence and/or atomic coordinate/x-ray diffraction data of the present invention, *e.g.*, the amino sequence provided in Figures 13-15, a representative fragment thereof, or an amino acid sequence having at least 80-100% overall identity to a 5-542 amino acid fragment of an amino acid sequence of Figures 13-15. Such a method provides the amino acid sequence and/or atomic coordinate/x-ray diffraction data in a form which allows a skilled artisan to analyze and determine the three- dimensional structure of a PPCA, a pPPCA or a subdomain thereof.

In one application of this embodiment, PPCA, pPPCA, or at least one subdomain thereof, amino acid sequence and/or atomic coordinate/x-ray diffraction data of the present invention is recorded on computer readable media. As used herein, "computer readable media" refers to any medium which can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as optical discs or CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. A skilled artisan can readily appreciate how any of the presently known computer readable media can be used to create a manufacture comprising computer readable medium having recorded thereon an amino acid sequence and/or atomic coordinate/x-ray diffraction data of the present invention.

As used herein, "recorded" refers to a process for storing information on computer readable medium. A skilled artisan can readily adopt any of the presently known methods for recording information on computer readable medium to generate manufactures comprising an amino acid sequence and/or atomic coordinate/x-ray diffraction data information of the present invention.

A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon an amino acid sequence and/or atomic coordinate/x-ray diffraction data of the present invention. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the sequence and x-ray data information of the present invention on computer readable medium. The sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and MICROSOFT Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like. A skilled artisan can readily adapt any number of dataprocessor structuring formats (e.g. text file or database) in order to obtain computer readable medium having recorded thereon the information of the present invention.

By providing on computer readable media having stored therein a PPCA or pPPCA sequence and/or atomic coordinates based on x-ray diffraction data, a skilled artisan can routinely access the sequence and atomic coordinate or x-ray diffraction data to model a PPCA, pPPCA, a subdomain thereof, or a ligand thereof. Computer algorithms are

publicly and commercially available which allow a skilled artisan to access this data provided on a computer readable medium and analyze it for structure determination and/or RDD. *See, e.g., Biotechnology Software Directory*, Mary Ann Liebert Publ., New York (1995).

The present invention further provides systems, particularly computer-based systems, which contain the sequence and/or diffraction data described herein. Such systems are designed to do structure determination and RDD for a PPCA, pPPCA or at least one subdomain thereof. Non-limiting examples are microcomputer workstations available from Silicon Graphics Incorporated and Sun Microsystems running Unix based, Windows NT or IBM OS/2 operating systems.

As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the sequence and/or atomic coordinate/x-ray diffraction data of the present invention. The minimum hardware means of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate which of the currently available computer-based system are suitable for use in the present invention. A monitor is optionally provided to visualize structure data.

As stated above, the computer-based systems of the present invention comprise a data storage means having stored therein a PPCA, pPPCA or fragment sequence and/or atomic coordinate/x-ray diffraction data of the present invention and the necessary hardware means and software means for supporting and implementing an analysis means. As used herein, "data storage means" refers to memory which can store sequence or atomic coordinate/x-ray diffraction data of the present invention, or a memory access means which can access manufactures having recorded thereon the sequence or x-ray data of the present invention.

As used herein, "search means" or "analysis means" refers to one or more programs which are implemented on the computer-based system to compare a target sequence or target structural motif with the sequence or x-ray data stored within the data storage means. Search means are used to identify fragments or regions of a PPCA or pPPCA which match a particular target sequence or target motif. A variety of known algorithms are disclosed publicly and a variety of commercially available software for conducting search means are and can be used in the computer-based systems of the present invention. A skilled artisan can readily recognize that any one of the available algorithms or implementing software packages for conducting computer analyses that can be adapted for use in the present computer-based systems.

As used herein, "a target structural motif," or "target motif," refers to any rationally selected sequence or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration or electron density map which is formed upon the folding of the target motif. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzymic active sites, structural subdomains, epitopes, functional domains and signal sequences. A variety of structural formats for the input and output means can be used to input and output the information in the computer-based systems of the present invention.

A variety of comparing means can be used to compare a target sequence or target motif with the data storage means to identify structural motifs or interpret electron density maps derived in part from the atomic coordinate/x-ray diffraction data. A skilled artisan can readily recognize that any one of the publicly available computer modeling programs can be used as the search means for the computer-based systems of the present invention.

One application of this embodiment is provided in Figure 22. Figure 22 provides a block diagram of a computer system 102 that can be used to implement the present invention. The computer system 102 includes a processor 106 connected to a bus 104. Also connected to the bus 104 are a main memory 108 (preferably implemented as random access memory, RAM) and a variety of secondary storage memory 110, such as a hard drive 112, a removable storage medium 114, and a monitor 120. The removable medium storage device 114 may represent, for example, a floppy disk drive, a CD-ROM drive, a magnetic tape drive, etc. A removable storage medium 116 (such as a floppy disk, a compact disk, a magnetic tape, etc.) containing control logic and/or data recorded therein may be inserted into

the removable medium storage medium 114. The computer system 102 includes appropriate software for reading the control logic and/or the data from the removable medium storage device 114 nce inserted in the removable medium storage device 114.

Amino acid, encoding nucleotide or other sequence and/or atomic coordinate/x-ray diffraction data of the present invention may be stored in a well known manner in the main memory 108, any of the secondary storage devices 110, and/or a removable storage device 116. Software for accessing and processing the amino acid sequence and/or atomic coordinate/x-ray diffraction data (such as search tools, comparing tools, etc.) reside in main memory 108 during execution. The monitor 120 is optionally used to visualize the structure data.

Structure Determination

One or more computational steps, computer programs and/or computer algorithms are used to build a molecular 3-D model of a PPCA or pPPCA, using amino acid sequence data from Figures 13-15 (or variants thereof) and/or atomic coordinate/x-ray diffraction data, as presented herein.

In x-ray crystallography, x-ray diffraction data and phases are combined to produce electron density maps in which the three-dimensional structure of a PPCA or pPPCA is then built or modeled. This structure can then be used for RDD of modulators of at least one PPCA- or pPPCA-related activity that is relevant to at least one PPCA- or pPPCA-related pathology.

Density Modification and Map Interpretation. Electron density maps can be calculated using such programs as those from the CCP4 computing package (SERC (UK) Collaborative Computing Project 4, Daresbury Laboratory, UK, 1979). Cycles of two-fold averaging can further be used, such as with the program RAVE (Kleywegt & Jones, Bailey *et al., eds., First Map to Final Model*, SERC Daresbury Laboratory, UK, pp 59-66 (1994)) and gradual model expansion. For map visualization and model building a program such as "O" (Jones (1991), *infra*) can be used.

Refinement and Model Validation. Rigid body and positional refinement can be carried out using a program such as X-PLOR (Brünger (1992), *infra*), *e.g.*, with the stereochemical parameters of Engh and Huber (*Acta Cryst. A47*:392-400 (1991)). If the model at this stage in the averaged maps still misses residues (*e.g.*, at least 5-10 per subunit), the some or all of the missing residues can be incorporated in the model during additional cycles of positional refinement and model building. The refinement procedure can start using data from lower resolution (*e.g.*, 25-10Å to 10-3.0 Å and then gradually extended to include data from 12-6Å to 3.0-1.5 Å. B-values (also termed temperature factors) for individual atoms can be refined once data of 2.8Å or higher (*e.g.*, up to 1.5 Å) has been added. Subsequently waters can be gradually added. A program such as ARP (Lamzin and Wilson, *Acta Cryst. D49*:129-147 (1993)) can be used to add crystallographic waters and as a tool to check for bad areas in the model. Programs such as PROCHECK (Lackowski *et al., J. Appl. Cryst. 26*:283-291 (1993)), WHATIF (Vriend, *J. Mol. Graph. 8*:52-56 (1990)) and PROFILE 3D (Lüthy *et al., Nature 356*:83-85 (1992)), as well as the geometrical analysis generated by X-PLOR can be been used to check the structure for errors. A program such as DSSP can be used to assign the secondary structure elements (Kabsch and Sander (1983), *infra*).

The structure of a PPCA or pPPCA can thus be solved with the molecular replacement procedure such as by using X-PLOR (Brünger (1992), *infra*). A partial search model for the monomer can be constructed using a related protein, such as wheat serine carboxypeptidase structure (Liao *et al.* (1992), *infra*). The rotation and translation function can be solved to yield orientations and positions for the subunits in the crystallographic asymmetric unit. This allows phases to be determined that, when combined with information from the x-ray diffraction patterns, allows electron density maps of a PPCA or pPPCA to be calculated. The atomic model is then built using these electron density maps. Cyclical two-fold density averaging can also be done to improve the electron density maps using a suitable program (*e.g.*, RAVE) and model expansion can also be used to add missing residues for each monomer, resulting in a model with 95-99.9% of the total number residues. The model can be refined in a program such as X-PLOR (Brünger (1992), *supra*), to a suitable crystallographic R_{factor}. The model data is then saved on computer readable media for use in further analysis, such as rational drug design.

Rational Design of Drugs that Interact with the PPCA or pPPCA

The determination of the three-dimensional structure of a PPCA or pPPCA, as described herein, provides a basis for the design of new and specific ligands for the diagnosis and/or treatment of at least one PPCA- or pPPCA-related pathology.

Several approaches can be taken for the use of the crystal structure of a PPCA or pPPCA in the rational design of ligands of this protein. A computer-assisted, manual examination of the active site structure is optionally done. The use of software such as GRID (Goodford, *J. Med. Chem. 28*:849-857 (1985)) a program that determines probable interaction sites between probes with various functional group characteristics and the enzyme surface — is used to analyze the active site to determine structures of inhibiting compounds. The program calculations, with suitable inhibiting groups on molecules (*e.g.*, protonated primary amines) as the probe, are used to identify potential hotspots around accessible positions at suitable energy contour levels. Suitable ligands, as inhibiting or stimulating modulating compounds or compositions, are then tested for modulating activities of at least one PPCA or pPPCA .

A diagnostic or therapeutic PPCA or pPPCA modulating ligand of the present invention can be, but is not limited to, at least one selected from a nucleic acid, a compound, a protein, an element, a lipid, an antibody, a saccharide, an isotope, a carbohydrate, an imaging agent, a lipoprotein, a glycoprotein, an enzyme, a detectable probe, and antibody or fragment thereof, or any combination thereof, which can be detectably labeled as for labeling antibodies. Such labels include, but are not limited to, enzymatic labels, radioisotope or radioactive compounds or elements, fluorescent compounds or metals, chemiluminescent compounds and bioluminescent compounds. Alternatively, any other known diagnostic or therapeutic agent can be used in a method of the invention.

After preliminary experiments are done to determine the K_m of the substrate with each enzyme activity of a PPCA or pPPCA, the time-dependent nature of modulation of ligand K_i values are determined, (*e.g.*, by the method of Henderson (*Biochem. J. 127*:321-333 (1972)). For example, the substrate (or blank where appropriate) and enzyme are pre-incubated in buffer. Reactions are initiated by the addition of substrate. Aliquots are removed over a suitable time course and each quenched by addition into the aliquots of suitable quenching solution (*e.g.*, sodium hydroxide in aqueous ethanol). The concentration of product is determined, *e.g.*, fluorometrically, using a spectrometer . Plots of fluorescence against time can be close to linear over the assay period, and are used to obtain values for the initial velocity in the presence (V_i) or absence (V_o) of ligand. Error is present in both axes in a Henderson plot, making it inappropriate for standard regression analysis (Leatherbarrow, *Trends Biochem. Sci. 15*:455-458 (1990)). Therefore, K_i values are obtained from the data by fitting to a modified version of the Henderson equation for competitive inhibition:

$$Qr^2 + (E_t - Q - I_t)r - E_t = 0$$

where (using the notation of Henderson (*Biochem. J. 127*:321-333 (1972)):

$$Q = K_i\left(\frac{A_t - K_a}{K_a}\right) \quad \text{and} \quad r = \frac{V_o}{V_i}$$

This equation is solved for the positive root with the constraint that

$$Q = K_i((A_t + K_a) / K_a)$$

using PROCNLIN from SAS (SAS Institute Inc., Cary, North Carolina, USA) which performs nonlinear regression using least-square techniques. The iterative method used is optionally the multivariate secant method, similar to the Gauss-Newton method, except that the derivatives in the Taylor series are estimated from the histogram of iterations rather than supplied analytically. A suitable convergence criterion is optionally used, *e.g.*, where there is a change in loss function of less than 10^{-8}.

Once modulating ligands are found and isolated r synthesized, crystall graphic studies of the compounds complexed to a PPCA or pPPCA can be performed. As a non-limiting example, PPCA or pPPCA crystals are soaked for 2 days in 0.01-100 mM ligand and x-ray diffraction data are collected on an area detector and/or an image plate detector (*e.g.*, a Mar image plate detector) using a rotating anode x-ray source. Data are collected to as high a resolution as possible, *e.g.*, an inner limit of diffraction of 1.5-3.5Å. An atomic model of the inhibitor is built into the difference Fourier map ($F_{\text{inhibitor complex}} - F_{\text{native}}$). The model can be refined to adjust the atomic positions to improve the fit with the electron density maps, while maintaining correct stereochemical constraints. The model will preferably have low r.m.s. deviations from the ideal bond lengths, as well as for the angles, respectively, as well as a low R-factor (preferably less than about 25-35%, such as less than about 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, or 25%.

Direct measurements of enzyme inhibition provide further confirmation that the modeled ligands are modulators of at least one biological activity of a PPCA or a pPPCA . As a non-limiting example, a modification (Chong *et al., Biochim. Biophys. Acta 1077*:65-71 (1991)) of the fluorometric assay of Potier (*et al., Analyt. Biochem. 94*:287-296 (1979)) is optionally used to measure neuraminidase inhibition or stimulation, optionally including determination of inhibition constants (K_i). Other suitable PPCA activity assay include, *e.g.*, cathepsin A activity (Galjart *et al., J. Biol. Chem. 266*:14754-14762 (1991); Endothelin I deamidase activity (Jackman, *et al., J. Biol. Chem. 267*:2872-2875(1992); and tachykinin deamidase activity (Jackman, *et al., J. Biol. Chem. 265*:11265-11272 (1990)).

Ligands of a PPCA or pPPCA, based on the crystal structure of this enzyme, are thus also provided by the present invention. A PPCA or pPPCA ligand is any molecule, compound or composition that is capable of associating with a PPCA or pPPCA and optionally modulating at least one function or structural feature of a PPCA or pPPCA. Preferably, a PPCA or pPPCA ligand modulates at least one biological activity of a PPCA or pPPCA. Demonstration of clinically useful levels, *e.g.*, *in vivo* activity is also important. In evaluating PPCA or pPPCA inhibitors for biological activity in animal models (*e.g.*, rat, mouse, rabbit) using various oral and parenteral routes of administration are evaluated. Using this approach, it is expected that modulation of a PPCA or pPPCA occurs in suitable animal models, using the ligands discovered by structure determination and x-ray crystallography.

Evaluation of Therapeutic Potentials of Compositions via a PPCA Animal Model

The present invention also provides methods for identifying diagnostic or therapeutic ligands of PPCA or pPPCA via computer RDD, to treat a PPCA-related pathology. Generally, a method for determining the therapeutic or diagnostic use of a PPCA or pPPCA modulating ligand, to treat a PPCA related pathology, comprises the steps of administering a known dose of at least one ligand containing compositions to an animal model having a phenotype corresponding to a PPCA-related pathology, monitoring the appropriate biological or biochemical parameters, and comparing the results with treated animals to those of untreated animals. Results indicating the onset or presence of a PPCA related pathology are generally referred to herein as "symptoms" of the disease. *See., e.g.*, U.S. Appl. No. 08/397,693, filed March 2, 1995, which is entirely incorporated herein by reference.

Appropriate biological and biochemical parameters that reflect the onset and progression of a PPCA related pathology include, but are not limited to, (1) gross biological parameters, e.g., physical appearance (i.e., flattening of the face, rough haircoat and/or subcutaneous swelling in affected animals) or growth (reduced weight gain); (2) gross behavioral parameters, e.g., lack of coordination; (3) biochemical assays, e.g., assays of cathepsin A, N-acetyl-α-neuraminidase or β-galactosidase activities in primary cultures of skin fibroblasts or tissue homogenates; (4) histopathological studies (visceromegaly, i.e., enlarged liver and spleen; accumulation of secondary vacuoles in kidney tissues; etc.).

A first method of evaluating the therapeutic potential of a composition using the transgenic non-human animals of the invention comprises the steps of:

(1) Administering a known dose of the composition to a first non-human animal having a phenotype corresponding to a human PPCA related pathology;

(2) Detecting the time of onset of symptoms in the first non-human animal: and

(3) Comparing the time of onset of symptoms in the first non-human animal to the time of onset of symptoms in a second non-human animal having a phenotype corresponding to a human PPCA related pathology, which has not been exposed to the composition;

wherein a statistically significant delay in the time of nset of symptoms in the first non-human animal relative to the time of onset of the symptoms in the second non-human animal indicates the potential of the composition for treating a PPCA related pathology.

A second method of evaluating the therapeutic potential of a composition using the non-human animals of the invention comprises the steps of:

(1) Administering a known dose of the composition to a first non-human animal having a phenotype corresponding to a human PPCA related pathology at an initial time, t_0;

(2) Determining the extent of symptoms in the first non-human animal at a later time, t_1; and

(3) Comparing, at t_1, the extent of symptoms in the first non-human animal to the extent of symptoms in a second non-human animal having a phenotype corresponding to a human PPCA related pathology, which has not been exposed to the composition at t_0,

wherein a statistically significant decrease in the extent of symptoms at t_1 in the first non-human animal relative to the extent of the symptoms at t_1 in the second non-human animal indicates the potential of the composition for treating a PPCA related pathology.

In the above methods, the composition being tested may comprise a chemical compound administered by circulatory injection or oral ingestion. The composition being evaluated may alternatively comprise a polypeptide administered by circulatory injection of an isolated or recombinant bacterium or virus that is live or attenuated, wherein the polypeptide is present on the surface of the bacterium or virus prior to injection, or a polypeptide administered by circulatory injection of an isolated or recombinant bacterium or virus capable of reproduction within a non-human animal, and the polypeptide is produced within a non-human animal by genetic expression of a DNA sequence encoding the polypeptide. Alternatively, the composition being evaluated may comprise one or more nucleic acids, including a gene from the human genome or a processed RNA transcript thereof. Similarly, the composition being evaluated may comprise cells removed from a mammal and genetically engineered to overexpress a lysosomal protein or some other therapeutic polypeptide.

Once the PPCA modulating ligand has been shown to be effective in an animal model, it can then be tested in human clinical trials, according to known method steps.

In the above methods, delivery of the composition being tested to non-human animals is achieved via means appropriate for the composition being tested, e.g., by diet; by intermittent or continuous intravenous injection of one or more of the compositions or of a liposome (Rahman and Schein, in *Liposomes as Drug Carriers*, Gregoriadis, ed., John Wiley, New York (1988), pages 381-400; Gabizon, A., in *Drug Carrier Systems*, Vol. 9, Roerdink *et al.*, eds., John Wiley, New York (1989), pages 185-212) or microparticle (Tice *et al.*, U.S. Patent 4,542,025 (Sep. 17, 1985)) formulation comprising one or more of the compositions; via subdermal implantation of drug-polymer conjugates (Duncan, R., *Anti-Cancer Drugs* 3:175-210 (1992); via microparticle bombardment (Sanford *et al.*, U.S. Patent 4,945,050 (Jul. 31, 1990)); via infusion pumps (Blackshear and Rohde, in *Drug Carrier Systems*, Vol. 9, Roerdink *et al.*, eds., John Wiley, New York (1989), pages 293-310) or by other appropriate means known in the art (see, generally, *Remington's Pharmaceutical Sciences*, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, PA (1990)).

Pharmaceutical/Diagnostic Administration

Using compounds or compositions comprising at least one PPCA or PPCA modulating ligand, the present invention further provides a method for modulating the activity of a PPCA or pPPCA protein in a cell. In general, ligands (antagonists or agonists) which have been identified to inhibit or enhance the activity of at least one PPCA or pPPCA ligand can be formulated so that the ligand can be contacted with a cell expressing at least one PPCA or pPPCA

protein *in vivo*. The contacting of such a cell with such a ligand results in the *in vivo* modulation of at least one biological activity of a PPCA or pPPCA.

At least one PPCA or pPPCA modulating compound or composition f the invention can be administered by any means that achieve the intended purpose, using a suitable pharmaceutical composition or formulation. For example, administration can be by various parenteral routes such as subcutaneous, intravenous, intradermal, intramuscular, intraperitoneal, intranasal, intracranial, transdermal, or buccal routes. Alternatively, or concurrently, administration can be by the oral route. Parenteral administration can be by bolus injection or by gradual perfusion over time.

A typical regimen for treatment or prophylaxis comprises administration of an effective amount over a period of one or several days, up to and including between one week and about six months. It is understood that the dosage of a diagnostic/pharmaceutical compound or composition of the invention administered *in vivo* or *in vitro* will be dependent upon the age, sex, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the diagnostic/ pharmaceutical effect desired. The ranges of effective doses provided herein are not intended to be limiting and represent preferred dose ranges. However, the most preferred dosage will be tailored to the individual subject, as is understood and determinable by one skilled in the relevant arts. See, *e.g.*, Berkow *et al.*, eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Goodman *et al.*, eds., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th edition, Pergamon Press, Inc., Elmsford, N.Y., (1990); *Avery's Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics*, 3rd edition, ADIS Press, LTD., Williams and Wilkins, Baltimore, MD. (1987), Ebadi, *Pharmacology*, Little, Brown and Co., Boston, (1985); Osol *et al.*, eds., *Remington's Pharmaceutical Sciences*, 18th edition, Mack Publishing Co., Easton, PA (1990); Katzung, *Basic and Clinical Pharmacology*, Appleton and Lange, Norwalk, CT (1992), which references are entirely incorporated herein by reference.

The total dose required for each treatment can be administered by multiple doses or in a single dose. The diagnostic/pharmaceutical compound or composition can be administered alone or in conjunction with other diagnostics and/or pharmaceuticals directed to the pathology, or directed to other symptoms of the pathology. Effective amounts of a diagnostic/pharmaceutical compound or composition of the invention are from about 0.1 µg to about 100 mg/kg body weight, administered at intervals of 4-72 hours, for a period of 2 hours to 1 year, and/or any range or value therein.

The recipients of administration of compounds and/or compositions of the invention can be any mammals. Among mammals, the preferred recipients are mammals of the Orders Primata (including humans, apes and monkeys), Arteriodactyla (including horses, goats, cows, sheep, pigs), Rodenta (including mice, rats, rabbits, and hamsters), and Carnivora (including cats, and dogs). The most preferred recipients are humans.

Having now generally described the invention, the same will be more readily understood through reference to the following example which is provided by way of illustration, and is not intended to be limiting of the present invention.

Example 1: Preparation, Purification and Crystallization of PPCA or pPPCA from Human Cells

The present invention provides, in one aspect, the determination of the three-dimensional structure of the human protective protein/cathepsin A (PPCA) in the precursor form (pPPCA) by a combination of molecular replacement and twofold density averaging. The structure presented here is the first of an enzyme associated with a human PPCA related pathology, and the third human lysosomal enzyme structure determined. The structure gives us insight into the zymogen activation mechanism of pPPCA , as well as the expected 3-D structure of PPCA and its specific and new enzymatic activities.

PPCA and pPPCA Expression and Purification

Plasmid Constructs. AcMNPV transfer-plasmids pJR2 and pBC3 (Figure 1) were derivatives of plasmid pAc373, carrying the entire polyhedrin gene (Smith *et al.*, 1985). In pJR2 a polylinker with a number of multiple cloning sites (MCS) was inserted directly 3' of the polyhedrin promoter, and substituted a 33-nucleotide deletion of the

polyhedrin gene, starting with the ATG. pBC3 had the polylinker situated in a similar position as pJR2, but instead of the 33-nt deletion this plasmid featured an ATG codon mutated in ACG. Full-length human PPCA cDNA, PPCA54 (Galjart *et al.*, 1988), and the two deletion cDNA mutants, 32(Δ20) and 20(Δ32) (Galjart *et al.*, 1991), were subcloned either in pJR2 or pBC3 as EcoRI fragments, using standard procedures (Sambrook *et al.*, 1989). (Figure 1). The 20(Δ32) deletion mutant was tagged with the human PPCA signal sequence, as reported earlier (Galjart *et al.*, 1991). All cDNA fragments were engineered to have short 3' and 5' untranslated regions (< 10 bp).

Transfection and Selection of Recombinant Baculovirus. Spodoptera frugiperda insect cells (IPLB-SF21) were cultured in monolayers at 27°C in TNM-FH medium (Hink, 1970), supplemented with 10% FBS and antibiotics (complete medium). Wild-type (wt) AcMNPV virus strain E2 (Smith and Summers, 1978) and recombinant baculoviruses were propagated on confluent monolayers of Sf2l cells. Recombinant constructs AcPPCA54, AcPPCA32 and AcPPCA20 were generated by cotransfecting Sf2l cells with 1 μg wt-AcMNPV DNA and 10 μg plasmid DNA, using the calcium phosphate method, modified for insect cells (Graham *et al.*, 1973; Carstens *et al.*, 1980; Summers *et al.*, 1987). Recombinant polyhedrin-negative recombinant baculoviruses were then selected and purified by sequential plaque assays, and verified by dot blot and southern blot analysis (Summers *et al.*, 1987). Large quantities of inoculum were produced by infection of insect cells at 25-50 % confluency, with recombinant virus at a multiplicity of infection (MOI) of < 1 pfu/cell. After 3 to 6 days at 27°C, when all cells appeared infected, the medium was harvested and centrifuged for 5 m at 1000 rpm to remove detached cells. The titre of the inoculum was determined by plaque assay analysis.

Protein purification and western blotting. Sf2l cells were cultured in either 175 CM^2 or 500 CM^2 flasks (triple flask, Nunc) to near confluency, and infected with recombinant baculoviruses at a MOI of 5-10 pfu/cell After 1.5 h incubation at 27 °C, the inoculum was replaced with complete medium for additional 8 to 10 hrs. Cell monolayers were then rinsed with PBS and cultured further for 38 h in unsupplemented Grace's medium. After infection the medium was collected, centrifuged for 5 m at 1500 g, and for 1 h at 100.000 g (Beckmann SW-28 rotor) to remove virus particles. After centrifugation the supernatant was concentrated 20-fold, in an Amicon stirred cell. Glycoproteins were purified ~60% using a concanavalin A-SEPHAROSE affinity chromatography column, as described earlier (Verheijen *et al.*, 1982). Total protein concentration was measured using the method of Smith *et al.*, (1985). Aliquots of the purified preparation were resolved on 12.5% SDS-polyacrylamide gels under reducing and non-reducing conditions. Gels were either Coomassie brilliant blue- or silver stained (Sambrook *et al.*, 1989). For western blotting, proteins were transferred from gels to IMMOBILON PVDV membranes (Millipore Corp.), using a semidry blotter (The W.E.P. company).

Development and Use of pPPCA antibodies. A 15 amino acid peptide (NH_2-Cys-Met-Trp-His-Gln-Ala-Leu-Leu-Arg-Ser-Glu-Asp-Lys-Ala-Arg-COOH) (Figure 5), based on the C-terminal sequence of the 34-kDa PPCA subunit (amino acid 285-298, Galjart *et al.*, 1988), was synthesized on a peptide synthesizer (Applied Biosystems), and covalently linked to the carrier protein *Keyhole Limpet Hemocyanin*, using the IMJECT ACTIVATED IMMUNOGEN CONJUGATION KIT (Pierce). Polyclonal antibodies against the conjugated product were raised in rabbit, by multiple subdermal injections of the protein (40-125 μg) mixed with incomplete Freunds adjuvant (Pierce). Rabbits were bled 34 days after the first injection. The antibodies, designated anti-pep, were tested on immunoblots and by immunoprecipitations of baculovirus produced PPCA.

Blots were incubated for at least 12 h in blocking buffer (0.01 M tris-buffered saline pH 8.0 (TBS), 0.05% Tween 20, and 3% (w/v BSA), and subsequently probed for 2 h with polyclonal PPCA antibodies, anti-54, diluted 1:200 in fresh blocking buffer. They were then washed for 1 h in TBS, 0.05% Tween 20, and incubated for 2 h with alkaline phosphatase conjugate anti-rabbit IgG (Sigma, 1:1000 in blocking buffer). Proteins were visualized using alkaline phosphatase substrate (Sigma, 4-aminodiphenylamine diazonium sulfate, naphtol as-mx phosphate).

Crystallization of PPCA. Fractions containing the precursor form of the protein as assayed on an SDS-PAGE gel were pooled. Subsequently the protein was concentrated to 5 mg/ml and the buffer exchanged to 50 mM NaAc pH 5.2 or 50 mM MES pH 6.5 using a CENTRICON-1 0. Crystals were grown using the hanging drop vapor diffusion

technique. Crystals suitable for data collection were grown using a reservoir solution containing : 2-10 % PEG 8000, pH 8.0 - 8.3, 50mM TRIZMA, 1mM NaN_3, 0.25 % β-octyl glucoside at 4-12°C. Mixing non-equal volumes of protein solution (in the range 5-10μl) and reservoir solution (in the range 2-6 W) enhanced the occurrence of single large crystals per drop under these crystallization conditions. The concentration of the protein solution before mixing was 5 mg/ml. Crystal growth was enhanced by macrocrystallization techniques (anything that promotes growth of big crystals) and in some cases by micro- and macroseeding techniques.

Example 2: Structure Determination of a pPPCA Crystallized from Human Cells

Data Collection, Data Processing and Reduction.

To allow for data collection at cryotemperatures, the crystals were cryoprotected by adding glycerol in 5% -10% steps to a solution of about 12% PEG 8000, 50 mM TRIZMA, pH 8.0, 1mM NaN_3, 0.25% β-octyl glucoside, which served as an artificial mother liquor. The crystals were incubated for half an hour at 40°C after each addition of glycerol. The final mother liquor contained 30% glycerol. Gradually increasing the glycerol was needed to help keep the crystals from cracking.

Diffraction data was collected at the Stanford Synchrotron Radiation Laboratories (SSRL) to 2.0 Å at -178°C on a MAR imaging plate at a wavelength of 1.08 Å on beam-line 7-1. The diffraction coordinate data (corresponding to atomic coordinates monomer 1, the other monomer coordinates are provided by matrix conversion of these coordinates, as presented herein) was processed and reduced using MOSFLM version 5.2 from the CCP4 program package (SERC (UK) Collaborative Computing Project 4, Daresbury Laboratory UK, 1979). The program REFIX (Kabsch (1993), *infra*) was used for auto-indexing. Using the CCP4 program suite (SERC (UK) Collaborative Computing Project 4, Daresbury Laboratory UK, 1979), the intensities were scaled (ROTAVATA), merged (AGROVATA) then converted to amplitudes and truncated with the program TRUNCATE. Statistics of the data collected are given in Table 1. The V_m (Matthews, B.W., *J. Mol. Biol. 33*:491-497 (1968)) is 3.2 $Å^3$/Da for 2 monomers in the asymmetric unit, corresponding to a solvent content of 62%.

Molecular Replacement

Search Model: The best molecular replacement results were obtained using a multi-Ala core as a search probe. The 'multi-Ala core' search model was constructed from the atomic coordinates of the CPW monomer (Liao et al., 1992), based on the sequence alignment as presented in Figure 15. Regions expected to deviate in structure between PPCA and CPW were deleted from the model (i.e. with low sequence identity or located in loops). The 125 residues identical in PPCA and CPW were left in the model; 112 residues were truncated to alanine. The remaining 94 residues through differing between CPW and PPCA, were considered sufficiently similar in size and the CPW residue left as such in the model. The resulting 'multi-Ala core' monomer consisted of 331 residues, constituting a large portion of the core domain and little atomic information for the 'cap' domain (see Figure 1). The model contained 30% of the expected protein scattering mass given the fact that there are two monomers in the asymmetric unit. The sequence identity between this search model and the true PPCA structure was 37.7%.

Rotation Function, PC Refinement and Translation Function: Native data of 8 - 4Å was used in the molecular replacement calculations. The rotational searches utilized a real space Patterson search method, as implemented in X-PLOR (Steigeman, 1974; Huber, 1985, Brünger 1992a) with a Patterson vector cutoff of 21Å. The self-rotation function failed to reveal any non-crystallographic two-fold symmetry relating two monomers in the asymmetric unit. In addition, the native self Pattersons did not reveal the presence of a non-crystallographic two-fold axis parallel to a crystallographic axis. These results indicated that the two monomers in the asymmetric unit might not form a dimer together. The cross-rotation function was carried to find the orientation of the two monomers in the asymmetric unit as follows. Patterson vector sets were calculated for the search model and the native data and the 8000 strongest Patterson vectors were used in the rotation function. The rotational space restricted to the asymmetric unit of the rotation function according to Rao et al., 1980, was sampled by rotating the Patterson vectors from the search model around Eulerian angles θ1, θ2, and θ3, while sampling θ2 in angular grid intervals of 2.5°. The 5000 highest rotation

function grid points were selected resulting from the product function of the two Patterson vector sets. The grid points (differing less than 8° around any given axis) were then clustered. The result was a list of 169 possible solutions for the rotation function, each corresponding to a set of three angles describing an orientation. The two top solutions were 3.9 and 3.8 sigma above the mean. PC-refinement (Brünger, 1990) was carried out to optimize each of the 169 possible solutions using the complete search model as a single rigid body. This yielded two orientations with a PC-index of 0.043 and 0.051 respectively. The orientations of these solutions were (D_1 = 261.4, D_2 = 36.22, D_3 = 147.28); and (D_1 = 18.52, D_2 = 47.40, D_3 = 23.22), respectively. In contrast, the rest of the possible solutions yielded an average PC-index of 0.022.

Individual translation function calculations were performed on a 1 Å grid. A translational solution was found for each orientation at positions (x=33.30, y=51.97, and z=12.79) and (x=25.23, y=28.58, and z=22.02), with respect to the crystallographic center, as 7.7 and 8.8σ, respectively, above the mean. The R_{factor} for the individual solutions was 55.6% and 54.8% in the resolution range 8.0 to 4.0Å, with a correlation coefficient (CC) of 0.095 and 0.114. A combined translation function was calculated to place each solution relative to the same crystallographic origin, resulting in an R_{factor} of 52.8% for data between 8.0 and 4.0Å, bringing the R_{factor} down to 51.3% and increasing the CC to 0.22. The molecular packing was assessed on a graphics workstation, which revealed no clashes between the placed search probes. However, a very large amount of empty space was present. The packing showed that the asymmetric unit contained two half dimers, each forming a dimer with another monomer in a neighboring unit cell. The two cores in the asymmetric unit were related by κ=73° around an axis tilted 15.5° off the crystallographic *a* axis lying in the *a,c* plane.

Iterative Model Building and Two-fold Averaging

Initial Electron Density Map: A $2m|F_{obs}| - D|F_{calc}|$ SigmaA weighted map (Read, 1986) was calculated using $|F_{calc}|$'s and phases from the molecular replacement solution. The map was contoured at 1σ and showed good density for most of the core. Density emerged for many side chains where the input model residue had been an Ala, indicating that the molecular replacement solution was correct.

First Model Built: The two rotated and translated search probes formed the starting point for model building of the PPCA precursor. The non-crystallographic symmetry (NCS) matrix was determined between the two cores using the "Lsq_explicit" option in the computer program O (Jones *et al.*, 1991). Subsequently a 'best monomer' was built by superimposing the electron densities from each monomer core, and adjusting the model accordingly. Residues were only incorporated in the model where the electron density was visible for the complete side chain. Residues from the search model for which no density was visible were removed. An alanine was built in the model at places where electron density for a side chain was partial. In this manner 294 residues, i.e. 65% of the C^{α} atoms were built in the 'best monomer' core. The second monomer was generated from the 'best monomer' model using the NCS operator relating the two monomers in the asymmetric unit. At this point the data set was partitioned in a working set and a test set consisting of 5% of the reflections between 8 - 2.2Å to monitor the R_{free} (Brünger et al. 1992b). The working data set was used for rigid body and positional refinement. For averaging and map calculations the unpartitioned data set was used. Twenty-five cycles of refinement using the two 'best monomers cores' positioned in the asymmetric unit as rigid bodies and data from 8.0 - 3.0Å, resulted in an R_{factor} of 53.5% for this resolution range. The atomic coordinates of this partial model were used to calculate a new $2m|F_{obs}| - D|F_{calc}|$ SigmaA weighted map which we called the 'best monomer map'.

Averaging: Search for Missing Density: The phasing power from the rigid body refined 'best monomer cores', consisting of 294 residues per core was insufficient to bring back interpretable electron density for the missing part of the model, 158 residues per monomer. To overcome this a 'bootstrapping' procedure was applied, entailing density averaging using RAVE (Kleywegt & Jones, 1994a) and model expansion. The 'best monomer map' and the rigid body refined 'best monomer cores' served as the starting point for this procedure.

Six bootstrapping cycles were carried out, called bmc1 thr ugh bmc6, allowing for the model to be extended in stepwise increments. Figure 16 sh ws a scheme of the steps incorporated in one bootstrapping cycle. After a cycle in which the model had undergone major expansion, a new molecular mask was calculated with MAMA (Kleywegt & Jones, 1994b) for use in the subsequent bootstrapping cycle. No phase recombination was applied between bootstrapping cycles. At the end of each cycle the inverted phases α_{inv} and inverted amplitudes F_{inv}'s were discarded. The NCS operator was re-optimized after cycle bmc3. The resolution range of the data included in the bootstrapping cycle started with 15 - 3.0 Å for bmc1 and was gradually extended to 15 - 2.7 Å in bmc6. The bootstrapping procedure is summarized in Table 2. To optimize the bootstrapping procedure, consideration was given to the molecular mask used in the averaging, the model building strategy and the refinement procedure.

Molecular masks: Four different masks were constructed in total. The atomic radius of all atoms was set to 4Å to calculate each mask. The masks were then manually modified using mask editing options in O (Jones *et al.* 1991). Mask1, was constructed around the 'best monomer core'. Subsequently it was greatly enlarged by multiple blocks of 10 - 15 $Å^3$ in the regions where the model was incomplete (Figure 17). This was crucial to prevent the density in the insertion area's from being flattened during the averaging step. Approximately one half of the dimer interface was estimated to be formed by regions from the missing cap domain. Major expansions of the mask in this area were made to accommodate for this. This resulted in a serious overlap problem when the mask was duplicated to cover a complete dimer. The mask was reduced where overlap occurred with the "overlap_trim" option of MAMA. After several bootstrapping cycles, new incorporated polypeptide fragments were carefully assigned to one of the two monomers forming the dimer and the mask at the dimer interface area's was manually adjusted accordingly. Essentially the masks were kept far too large in regions where the model was missing in order to avoid erroneous flattening of electron density. In contrast the masks were tightened around the area's of the molecule where the model was complete.

Model Building: A conservative model building strategy was adopted. Initially only side chains were mutated in the core region to fit the PPCA amino acid sequence and where the density was clear, poly-alanine fragments were built in the insertion area's (loops and the cap domain). Newly included atoms were given a B-factor of 20 $Å^2$. Only once models bmc5 and bmc6 were obtained, was the electron density of sufficient quality to allow side chains to be incorporated confidently in the cap domain (residues 190 - 303). At this stage the C^α trace was virtually complete for the whole dimer and the sequence could be fit unambiguously.

Refinement: Positional refinement was postponed until after 3 cycles of bootstrapping resulting in a final model containing 91% of the C^α atoms. Forty steps of positional refinement were then carried out to improve the geometry of the model. Subsequently only one of the refined monomer was taken and the other generated using NCS operators. The rational for delaying the positional refinement is addressed in the discussion.

Completing the model: deviations from two-fold symmetry. It was possible to add 148 residues and 185 side chains per monomer after a total of 6 bootstrapping cycles. At this stage, each subunit contained 442 residues and 413 side chains, i.e. 98% of the C^α and 91% of the side chains atoms. The gradual model expansion as a function of the bootstrapping cycle is shown in Figure 18.

Twenty residues were still missing in the asymmetric unit at this stage. These were localized to two stretches per monomer (260 - 262 and 287-292). With most of the scattering mass incorporated, the monomers from model bmc6 was refined individually with X-PLOR (Brünger, 1992a) in an attempt to retrieve electron density for the still missing residues. After 40 steps of positional refinement using data from 8.0 - 2.6 Å, the R_{factor} dropped significantly from 40.2% to 33.2%. The model was further positionally refined using a full weight W_A on the crystallographic term. The data included in the refinement was gradually extended to 2.2 Å. At 2.4 Å resolution individual B-factors were refined and the distribution checked as a function of atom location (*i.e.*, low B-factors in the core and high B-factors on the surface). Cycles of refinement and refitting allowed for 18 missing residues to be added. Essentially almost the complete cap domain was retrieved using the bootstrapping procedure, as shown in Figure 19. It became apparent from the refined maps that the two stretches of missing amino acids adopted a very different conformation in the two monomers (with

as much as an average r.m.s.d. of 7.9 Å for the C$^{\alpha}$s of residues 287 - 292). For this reason electron density for these regions had not been retrieved in the two-fold averaging process. The stepwise improvement of the electron density maps along with averaging, model expansion and refinement is shown in Figure 6.

The program ARP was used t check our model, in particular the region at the dimer interface (Lamzin & Wilson, 1993). Prior to the final round of positional refinement, an $|F_{obs}|/\sigma$ cutoff was applied to reject 10% of the weakest data as well as an anisotropic scale factor to offset the decreased resolution along the crystallographic a axis. The final model is of good geometry with a final R_{factor} of 21.3% (R_{free} of 26.8 %) for data between 8.0 and 2.2 Å (see Table 3). A Ramachandran plot is given in Figure 21. The r.m.s. coordinate error is 0.282 as calculated by SigmaA (Read, 1986). The average phase difference between the initial molecular replacement model and the currently refined model is calculated to be 71° for data between 10 - 2.2 Å.

The structure determination of PPCA is special in that two-fold averaging could be applied to refine very poor molecular replacement phases, enabling us to retrieve electron density for 148 residues and 185 side chains per monomer. In total 314 complete residues were added per asymmetric unit, equivalent to about 35 kDa of protein. In retrospect we feel that a number of factors contributed to a successful structure determination.

Crystal Packing. Each monomer in the crystal is interacting with four non-crystallographically related monomers. By far the most extensive contact is with a non-crystallographically related monomer generating the physiological dimer. Three additional contacts are extensive crystal contacts ranging from 200-800 Å^2 averaged per monomer. The largest nondimer crystal contact involves the precursor loops from two crystallographically independent monomers (region 265-267, 281-295 from monomer 1 with residues 281-293 from monomer 2) making intimate contact with each other. Summed together these loops create an intermolecular buried surface of 1680 Å^2. We believe that this stabilizes an otherwise very flexible area, possibly explaining the good diffraction qualities of the P2$_1$2$_1$2 crystals.

It is also in this crystal contact that we find deviating spacial conformation and secondary structure between the two monomers as mentioned before. The electron density in this region is of very good quality with average temperature factors of 16.6 Å^2 for main chain and 18.3 Å^2 for side chains.

pPPCA and the Hydrolase Family. The fold of pPPCA belongs to the large hydrolase fold family containing enzymes such as the serine carboxypeptidases, dehalogenase, various lipases and acetylcholine esterase (Ollis *et al.* (1992), *infra*), having various different catalytic functions. Though the central core is the same (a central β-sheet flanked by α-helices on both sides) the proteins in this family all seem to have different 'cap' domains, both with respect to fold as well as size (Figure 7A-F). pPPCA has one of the largest cap domains comprising 121 residues forming the three helical bundle of the helical subdomain and a three stranded β-sheet of the maturation subdomain.

Major Differences and Comparison With the Serine Carboxypeptidases. The overall fold of the pPPCA monomer is similar to that of the wheat and yeast serine carboxypeptidases (Endrizzi *et al.* (1994), *infra*; Ollis *et al.* (1992), *infra*). The complete core domains of pPPCA and CPW superimpose with an r.m.s. deviation of 1.7 Å for 302 Cα atoms and 38% sequence identity. Deleting major deviating loops from the core domain allows for pPPCA to superimpose with an r.m.s. deviation of 1.2 Å onto CPW and CPY (293 equivalent C$^{\alpha}$s with 40 % sequence identity for CPW/pPPCA and 271 equivalent C$^{\alpha}$s for CPY/pPPCA with 42.2% identity).

The cap domain in pPPCA differs significantly from the CPW and CPY counterparts. The pPPCA structure reveals a large maturation subdomain not present in the structure of CPW and CPY for which the structures of the enzymatically active forms are known. All three enzymes contain a 3 helical bundle in the cap domain. The sequence identity between the three proteins in this region is very low (ca. 12 %). In contrast, PPCA shows a much greater deviation. Hα1 superimposes reasonably well with the CPW counterpart maintaining the same general orientation with respect to the core domain (requiring a rotation of only 7.4°). But helices Hα2 and Hα3 have undergone major rotations with respect to Hα1 and the core domains by $\kappa = 28.5°$ and $\kappa = 93.4°$, respectively (Figure 8A).

Due to the integral role of the cap domain in forming the dimer interface, the dimers of PPCA and CPW were compared. In the pPPCA and CPW dimers the monomers are oriented differently with respect to each other.

Superposition of the core domain of one monomer from each dimer shows that the second pair of monomers (forming the respective dimers) differ by a remarkable 15° in orientation (Figure 8B). Thus, it appears that the extensive differences in the cap domains lead to a different arrangement of the subunits in the dimers of PPCA and CPW.

Catalytic Triad and Enzymatic Mechanism. Our structure shows that the precursor PPCA has all the elements proposed for the enzymatic machinery of the serine carboxypeptidase family (Liao *et al.* (1992), *infra*; Endrizzi *et al.* (1994), *infra*), and is now discovered to be the third structure elucidated belonging to this family of enzymes after CPW and CPY. The catalytic triad in the active site of pPPCA is formed by residues Ser 150, His 429 and Asp 372. The O^{γ} of Ser 150 forms a good hydrogen bond with the $N^{\epsilon}1$ of His 429 with a N to O distance of 2.8 Å. The $N^{\delta}1$ of His 429 is 2.7 Å removed from the $O^{\delta}2$ and 3.3 Å from the $O^{\delta}1$ of Asp 372. Further, two backbone amides appear to orient the carboxylate group of Asp 372. The N of Ala 374 is at a distance of 3.0 Å to the $O^{\delta 1}$ of Asp 372 and the N of Cys 375 is at a distance of 2.9 Å to the $O^{\delta 2}$ of Asp 372.

The oxyanion hole proposed to stabilize the negatively charged tetrahedral intermediate in serine carboxypeptidases is formed by the backbone amides of Gly 57 and Tyr 151 in PPCA. The 32 atoms of the catalytic triad residues plus the oxyanion hole amides from PPCA, CPY and CPW superimpose with an r.m.s. deviation of 0.4 Å indicating the very high degree of structural similarity of the active site in the PPCA precursor with those in the fully active enzymes CPY and CPW, (see Table 4). The carboxylate of Asp 372 and the imidazole of His 429 in PPCA are non-planar, making an angle of approximately 60° between the imidazole and the carboxylate. A similar non-planarity has been observed in CPW and CPY, in contrast to the planar orientation found in subtilisin-.and trypsin-type serine proteases (McPhalen *et al.*, *Biochemistry 27*:6582-6598 (1988)).

In pPPCA, a pair of glutamic acid residues (Glu 69 and Glu 149) is positioned near the catalytic triad, with their carboxylate groups interacting with each other. The carboxylate groups are located at approximately 8 Å from the O^{γ} of Ser 150, and lie at the bottom of the active site. An asparagine (Asn 55) is orientated such that it forms a hydrogen bond to each of the two carboxylate groups of the glutamic acid pair, at an $N^{\delta 2}$ (Asn) to $O^{\epsilon 1}/O^{\epsilon 2}$ (Glu) distance of 3.0 and 3.6 Å, respectively. In addition the two carboxylates interact with each other via hydrogen bonds. This configuration of two glutamic acid residues and an asparagine, is conserved between pPPCA, CPW and CPY (see Table 4), and has been implicated in regulating the low pH optimum for the carboxypeptidase activity found in the serine carboxypeptidases (Liao *et al.* (1992), *infra*). Biochemical data has suggested that a functional group with an apparent pK_a value of pH 5.5, functions to bind the C-terminal carboxylate group of peptide substrates and is responsible for the observed pH optimum of 5.5 (reviewed in Breddam *et al.* (1986), *infra*; Rawlings & Barrett (1994), *infra*). Together with their structural data, Liao and colleagues (Liao *et al.* (1992), *infra*) have suggested that at pH 5.5 or below, one or both glutamates must be uncharged, while at a pH higher than 5.5 one or both of the carboxylates which are orientated opposite to each other, may become deprotonated resulting in unfavorable electrostatic interactions. This would disturb the hydrogen bonding pattern or result in structural perturbations causing the observed increase in K_m for peptide substrates at high pH. In pPPCA the orientation of this pair of glutamic acids as well as that of the asparagine is essentially identical in structure to the equivalent residues in CPW and CPY (see Table 4), even though the structure has been determined at pH 8. The CPW and CPY structures have been determined at pH 5.7 and at pH 6.5-7.0. Thus, our structure appears to rule out large pH induced conformational changes of these three residues at least up to a pH value 2.5 units above that optimal for carboxypeptidase activity. However the high degree of conservation of these residues does indicate some role in a characteristic shared by all three enzymes.

From our comparison it is clear that the enzymatic machinery in the PPCA precursor form is in a conformation virtually identical to that found in the fully active CPW and CPY enzymes. On this basis, the conformation of the enzymatic machinery found in pPPCA is expected to faithfully represent the conformation that will be found in the active PPCA.

Active Site, Substrate Specificity. PPCA has a substrate preference for hydrophobic residues in the P1 and/or P1' binding pockets (Jackman *et al., Hypertension 21*:925-928 (1993)). In CPW the P1' pocket was identified to consist of two tyrosine residues (Tyr 60 and Tyr 239) which form a long channel, capped by two acidic residues (Glu 272 and Glu 398) at the end (Liao *et al.* (1992), *infra*). This explains the highest preference of this enzyme for Arg and Lys as the leaving group (Breddam *et al., Carlsberg Res. Commun. 52*:297-311 (1987)). In CPY a similarly shaped pocket is formed by the residues Thr 60, Tyr 256, Leu 272 and Met 398 (Endrizzi *et al.* (1994), *infra*). In PPCA the analogous residues are Tyr 247 and Asp 64, forming the sides of the pocket with at the far end Met 430 and Thr 304. This is reasonably consistent with an overall preference of PPCA for a hydrophobic leaving group.

Inactivation Mechanism of the Precursor Form. During the maturation step of the PPCA precursor form, at maximum residues 285-298 forming the 'excision' peptide, are removed by an as yet unidentified protease(s). *In vitro*, the maturation event can be mimicked by digestion with trypsin utilizing probably positions Arg 284, as well as Arg 292 and/or Arg 298. The residues forming the 'excision' peptide adopt distinctly different conformations in the two crystallographically distinct monomers forming the PPCA dimer in our crystal structure. Yet in both monomers this polypeptide region extends out from the protein surface and is virtually completely solvent and protease accessible (Figure 9). Arg 284 and Arg 292 are particularly well exposed. The main chain atoms of Arg 298 are less accessible, being sandwiched between the strand Mβ2 and a loop N-terminal to helix Cα6, while a salt bridge with Glu 264 renders the side chain atoms of Arg 298 partially solvent inaccessible.

The active site cleft is blocked by numerous residues from the maturation subdomain in the precursor form of PPCA. The catalytic triad is rendered solvent inaccessible by residues Asn 275, Ile 276 and Phe 277. These residues are part of the polypeptide Asp 272-Phe 277 which we call the 'blocking' peptide. This peptide is held down predominantly by hydrophobic contacts of Leu 273, Ile 276, and Phe 277 to the core domain residues Gly 57, Cys 60, Leu 180, Leu 190, Val 191, Leu 232, Val 235, Ile 246, Leu 280, Leu 282, Met 299 and Ala 373 (Fig 10). In addition residue Asn 275 of the blocking peptide appears to fill what might be part of the P1 binding pocket in the mature form. Further inspection of the blocking peptide suggests that Gly 274 with Ramachandran angles $\phi = 66°$ and $\phi = 28°$, might play a central role in the strand blocking the active site. A glycine at this position appears critical to allow the polypeptide chain to adopt a conformation with its main chain at a safe distance from the catalytic triad. This might aid in allowing the blocking peptide to assume a conformation resistant to autocatalysis. The P1' binding pocket seems to be beautifully filled by Pro 301 interacting with Thr 304, Tyr 247, Cys 60 and Cys 334. Thus substrate binding is not possible in the precursor form due to the inaccessibility of the substrate binding pockets.

We conclude that the inactivation mechanism of PPCA is based on blocking of the active site, and not upon changes in the position of functional groups involved in catalysis/transition state stabilization. Both the P1, P2 and P1' binding pockets are rendered solvent inaccessible. The function of the blocking peptide seems to be to render the catalytic triad as well as the region around the P1 and P2 binding pockets solvent inaccessible. The blocking peptide, however, does not assume a conformation that a peptide substrate would adopt. It is carefully positioned in a manner which is different from that of a productive substrate, thereby avoiding being by the nearby catalytic residues which are correctly poised for catalysis. A crucial observation is that the excision peptide itself does not bind in the active site cleft. Hence, mere removal of the excision peptide alone is not sufficient to allow solvent or substrate access to the active site.

Proposed Maturation Event and Extent of Conformational Rearrangement. The active site of the precursor of PPCA appears to be fully blocked by 49 residues of the maturation subdomain, as shown in Figure 11. Based on the precursor structure and the comparison with CPW and CPY it is proposed that a region comprising approximately residues 254-284 rearranges to free the P1, P2 binding sites, while the residues 299-302 rearrange to free the P1' binding pocket. The linker connecting these two segments of polypeptide chain is the 14 amino acid excision peptide Met 285-Arg 298. The extent of the residues rearranging is likely to be limited by a disulfide bridge Cys 253 and Cys 303, which

is conserved in the serine carboxypeptidase family. This critical disulfide serves to keep the secondary structure elements together at the far end of the PI' pocket.

An interesting pair of salt bridges is observed between Arg 262, Asp 300, Glu 264 and Arg 298, four residues located on strands Mβ1 and Mβ3 of the mixed β-sheet found in the maturation subdomain. This cluster of residues is strategically positioned at the base of the excision peptide, close the core domain and 'shielding' the mixed β-sheet via side chain interactions (see Figure 11). These residues are strictly conserved among the human, mouse and chicken PPCAs (Galjart *et al.* (1991), *infra*). This charge cluster may be effected by a shift from neutral to acidic pH. Arrival in the endosome/lysosome is expected to result in protonation of either the Asp or the Glu residue or both, resulting in unfavorable electrostatic interactions and destabilization of this charge cluster. This in turn is expected to promote partial unfolding of maturation subdomain, allowing easier access to additional potential cleavage sites, and stimulating removal of the 'blocking' peptide which fills the active site in the precursor.

A similar double salt bridge has been observed in the aspartic proteinase zymogen pepsinogen between the proenzyme segment (Arg 8P) and the enzyme (Arg 308, Glu 13, Asp 304).

The maturation mechanism for pPPCA appears to be novel among proteases for which the three-dimensional structure of the zymogen is known. The catalytic triad in the precursor form is in a catalytically competent conformation. Enzymatic activity is prevented by a 'blocking' peptide. The blocking peptide is however different from the excision peptide and does not get excised from the mature enzyme. This leads to the distinct difference with the other known maturation mechanisms in that, after disappearance of the excision peptide, up to 35 residues filling the active site cleft in the PPCA precursor must rearrange to render the catalytic triad solvent accessible (see Figure 12), but do not get cleaved off. Removal of the excision peptide, and possibly a shift to lower pH in the endosome/lysosome, appears to be a trigger for this event. The mechanism does not appear to be autocatalytic, as uptake experiments with cultured galactosialidosis fibroblasts, have shown that a mutant PPCA with the catalytic Ser 150 mutated to Ala, is properly targeted and processed. It retains its protective function and except for the loss of catalytic activity is biochemically indistinguishable from the wild type enzyme (Galjart *et al.* (1991), *infra*). Surprisingly, the maturation mechanism of the serine carboxypeptidases PPCA, CPW and CPY may all differ from each other as well. This is clearest for CPY, in which a 91 residue polypeptide is cleaved off N-terminally to convert the zymogen to an active enzyme (Winther and Sorensen, *Proc. Natl. Acad. Sci. USA 88*:9330-9334 (1991)), as opposed to the excision of a peptide from within the zymogen generating a two chain active form as is the case for PPCA and CPW.

Looking at the hydrolase fold family, the catalytic triad is housed in the core domain and the various cap domains attenuate the biological function by influencing entirely different properties such as: (I) enzyme kinetics exemplified by the interfacial activation of lipases (Smith *et al., Curr. Opinion in Structural Biology 2*:490-496 (1992)); (ii) substrate channeling as is proposed for acetylcholine esterase (Sussman *et al.* (1991), *infra*); (iii) substrate recognition, proposed for dehalogenase by (Franken *et al.* (1991), *infra*) and for CPY and CPW by (Endrizzi *et al.* (1994), *infra*); and (iv) enzyme inactivation in the case of PPCA.

Biological Implications. Deficiency of the protective protein/cathepsin A (PPCA) in humans results in the lysosomal storage disease galactosialidosis. PPCA is thought to form a multi-enzyme complex with β-galactosidase and neuraminidase in the lysosomes protecting the latter glycosidases in their harsh acidic and proteases-rich environment. PPCA has a 30% sequence identity to the wheat serine carboxypeptidase (CPW) and yeast serine carboxypeptidase (CPY). It has been show that PPCA in the precursor form is inactive, but upon maturation, entailing excision of a 2 kDa peptide, carboxypeptidase activity is released.

The precursor structure reveals an inactivation mechanism that has not been seen before in any of the other known zymogen structures of proteases (available for the serine-, metallo- and aspartic protease classes). The catalytic triad seems to have an arrangement poised for catalysis. However, the triad is rendered solvent and substrate inaccessible by a strand from the maturation subdomain binding in the active site cleft. Surprisingly, this strand called the 'blocking' peptide does not overlap with the 2 kDa 'excision' peptide. Hence, after removal of the excision peptide

up to 35 additional residues must rearrange in order to unblock the active site cleft. A strategically positioned pair of salt bridges, comprising Arg 262, Arg 298, Glu 264, and Asp 300 at the base of the excision peptide, are expected to optionally become destabilized at low pH, unraveling this region of the structure, allowing easier access to cleavage sites and/or promoting the rearrangement event.

A number of research groups are currently involved in designing enzyme and gene therapy procedures for several lysosomal storage diseases. Insight into the three-dimensional structure, protein functioning and stability of PPCA, the first enzyme of known structure associated with a lysosomal storage disease and the third human lysosomal structure to be determined, may prove useful in future designs of an adequate therapy procedure for galactosialidosis. Information from the three-dimensional structure of PPCA, might also aid in designing an engineered form of PPCA with increased stability and a longer half-life.

Table 1: X-ray Data Collection Statistics

resolution	32.27-2.2 Å
wavelength	1.08 Å
space group	$P2_12_12$
unit cell	a=115.04 b =148.11 c=80.97 Å
temperature of data collection	-178°C
No. of observed reflections	436,709
No. of unique reflections	67,740
completeness of all data	95.7%
R_{sym} for all data	5.1%
completeness of outer shell (2.26-2.20Å)	87.0%
R_{sym} in outer shell (2.26-2.20Å)	13.0%

$R_{sym}=\sum\sum I_i(h)-<I(h)>/\sum\sum I_i(h)$, where $I_i(h)$ is the i^{th} observation for reflection h and $<I(h)>$ is the weighted mean of all the observations.

Table 2: Course of Model Building

Model	nr. f C^{α}s	nr. f side chains	V_{mask} (10^4 Å^3)	Rfact r	R_{free}	CC	CC_{free}
				{statistics using data between 8.0 and 3.0Å}			
mol. repl. (mr)							
rigid body ref. (rmr)	331	125	-	54.2	55.3	0.243	0.244
calculate NCS matrix				52.6	52.9	0.287	0.318
best monomer (bm)							
rigid body ref.	294	228	-	55.9	57.4	0.228	0216
update NCS matrix				53.5	55.0	0.320	0328
bmc1 (mask 1)	373	258	10.8	49.9	51.3	0.403	0.424
bmc2 (mask 1)	405	277	10.8	48.6	48.4	0.443	0.478
bmc3 (mask 2)							
rigid body ref.	411	307	9.99	47.1	48.6	0.471	0.491
positional ref. (pbmc3)				46.9	48.4	0.476	0.492
update NCS matrix				39.4	44.7	0.622	0.562
bmc4 (mask 1)	412	327	10.8	41.7	43.1	0.584	0.585
bmc5 (mask 3)	435	387	8.88	39.8	40.6	0.621	0.623
bmc6 (mask 4)	442	413	9.11	38.4	40.2	0.647	0.637

Summary of the bootstrapping procedure. The resulting models have been listed chronologically starting with the molecular replacement solution, *i.e.* mr (molecular replacement), bm (best monomer core), and the bootstrapping cycles bmc1 through bmc6. The following statistics are given for the various models: the number of C^{α} atoms built per monomer; the number of correct side chains incorporated per monomer and the volume of the molecular mask used during the averaging if applicable. The quality of each model is assessed using the R_{factor}, R_{free}, CC and CC_{free} calculated by X-PLOR for data between 8.0 and 3.0 Å. After positional refinement of model bmc3, both monomers were made equivalent by taking one monomer and generating the non-crystallographically related one.

Table 3: Current Status of the Model

statistics for the data used in refinement:		
resolution (Å)	Rfactor (%)	completeness (%)
8.0 - 4.3	22.4	85.7
4.3 - 3.5	19.0	89.1
3.5 - 3.0	20.6	89.1
3.0 - 2.8	21.3	87.9
2.8 - 2.6	22.3	86.1
2.6 - 2.4	22.2	84.0
2.4 - 2.3	22.7	81.3
2.3 - 2.2	24.0	78.3
8.0 - 2.2. Å	21.3%	
model:		
molecules in the asymmetric unit:		2
residues (out of 904 possible):		902
sugars:		6
waters:		296
r.m.s.d. bond length (Å):		0.012
r.m.s.d. bond angles (°):		1.72
average B-values for main chain atoms (Å^2):		16.6
side chain atoms (Å^2):		18.3

Table 4

Superposition of the proposed catalytic machinery of the serine carboxypeptidases with known three-dimensional structure PPCA, CPW (Liao *et al.*, *Biochemistry 31*:9796-9812 (1992)) and CPY (Endrizzi *et al.*, *Biochemistry 33*:11106-11120 (1994)).

PPCA		CPW		ΔPPCA-CPW (Å)	CPY		ΔPPCA-CPW (Å)
Catalytic triad:	N	Ser 146	N	0.3	Ser 146	N	0.4
Ser 150	C^{α}		C^{α}	0.4		C^{α}	0.5
	C	His 397	C	0.3	His 397	C	0.4
His 429	O		O	0.3		O	0.4
	C^{β}		C^{β}	0.9		C^{β}	1.1
	O^{γ}	Asp 338	O^{γ}	1.5	Asp 338	O^{γ}	0.9
Asp 372	N		N	0.2		N	0.4
	C^{α}		C^{α}	0.3		C^{α}	0.4
	C		C	0.3		C	0.5
	O		O	0.5		O	0.6
	C^{β}		C^{β}	0.3		C^{β}	0.6
	O^{γ}		O^{γ}	0.3		O^{γ}	0.5
	$C^{\delta 2}$		$C^{\delta 2}$	0.7		$C^{\delta 2}$	0.5
	$C_{\epsilon 1}$		$C_{\epsilon 1}$	0.4		$C^{\epsilon 1}$	0.5
	$N^{\delta 1}$		$N^{\delta 1}$	0.3		$N^{\delta 1}$	0.4
	$N_{\epsilon 2}$		$N_{\epsilon 2}$	0.7		$N^{\epsilon 2}$	0.5
	N		N	0.2		N	0.2
	C^{α}		C^{α}	0.1		C^{α}	0.1
	C		C	0.1		C	0.1
	O		O	0.2		O	0.1
	C^{β}		C^{β}	0.3		C^{β}	0.2
	C^{γ}		C^{γ}	0.2		C^{γ}	0.1
	$O^{\delta 1}$		$O^{\delta 1}$	0.2		$O^{\delta 1}$	0.3
	$O^{\delta 2}$		$O^{\delta 2}$	0.4			0.1
Proposed oxyanion hole (formed by two backbone amides):							
Gly 57	N	Gly 53	N	0.1	Gly 53	N	0.5
Tyr 151	C^{α}	Tyr 147	C^{α}	0.2	Tyr 147	C^{α}	0.4
	C		C	0.1		C	0.4
	O		O	0.3		O	0.8
	N		N	0.3		N	0.2
	C^{α}		C^{α}	0.2		C^{α}	0.1
	C		C	0.3		C	0.2
	O		O	0.5		O	0.2
proposed regulation of pH dependent peptidase activity:							
Asn 55	averaged over all atoms		Asn 51	0.2		Asn 51	0.2
Glu 69	averaged over all atoms		Glu 65	0.3		Glu 65	0.7
Glu 149	averaged over all atoms		Glu 145	0.4		Glu 145	0.4

The residues forming the proposed catalytic machinery are strictly conserved between the three serine carboxypeptidases. The deviation in distance between the atoms from PPCA and the equivalent atoms in CPW or CPY after superposition is given in Angstrom.

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What Is Claimed Is:

1. A method for crystallizing a human protective protein/cathepsin A (PPCA) or precursor human protective/cathepsin A protein (pPPCA), comprising

(a) providing a purified PPCA or pPPCA;

(b) crystallizing the purified PPCA or pPPCA using a hanging drop or diffusion method, to provide crystallized PPCA or pPPCA having biological activity,

wherein the crystallized PPCA or pPPCA is resolvable using x-ray crystallography to obtain x-ray diffraction patterns suitable for three-dimensional structure determination of the PPCA or pPPCA.

2. A method according to claim 1, wherein said PPCA or pPPCA has at least one biological activity selected from the group consisting of enzyme protecting activity, enzyme modulating activity and peptide hydrolyzing activity.

3. A method according to claim 1, wherein said crystallization step is done under conditions of purified PPCA or pPPCA; 2-30% PEG400-10,000; precipitating salt; buffers, and pH 7-9.

4. A method according to claim 3, wherein the crystallization conditions are PPCA or pPPCA; 5-14% PEG8000, 40-80 mM tromethamine, 0.05-2.0 mM NaN_3 and pH 8.0-8.3.

5. A crystallized PPCA or pPPCA, or at least one subdomain thereof, provided by a method according to claim 1.

6. A method for providing an atomic model of a PPCA or pPPCA, comprising

(a) providing a computer readable medium having stored thereon atomic coordinate/x-ray diffraction data of said PPCA or pPPCA in crystalline form, said data sufficient to model the three-dimensional structure of said PPCA, said pPPCA, or at least one subdomain thereof;

(b) analyzing, on a computer using at least one subroutine executed in said computer, the atomic coordinate/x-ray diffraction data from (a) to provide data output defining an atomic model of said PPCA or said pPPCA, said analyzing utilizing at least one computing algorithm selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(c) obtaining atomic model output data defining the three-dimensional structure of said PPCA, pPPCA or at least one subdomain thereof.

7. A method according to claim 6, wherein said computer readable medium further has stored thereon data corresponding to a nucleic acid sequence or an amino acid sequence data comprising at least one structural domain or a functional domain of a PPCA or pPPCA corresponding to a portion of the amino acid sequences of Figures 13 or 14, and wherein said analyzing step further comprises analyzing said sequence data.

8. A computer readable medium having stored thereon atomic model data of said PPCA or pPPCA as the model output data produced by a method according to claim 6.

9. A computer-based system for providing atomic model data of the three dimensional structure of a PPCA or a pPPCA, comprising the following elements;

(a) a computer readable medium having stored thereon atomic coordinate/x-ray diffraction data of said PPCA or pPPCA or at least one subdomain thereof;

(b) at least one computing subroutine, that when executed in a computer, causes the computer to analyze the atomic coordinate/x-ray diffraction data from (a) to provide data output defining an atomic model of said PPCA or pPPCA, said analyzing utilizing at least one computing subroutine selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(c) retrieval means for obtaining atomic model output data defining the three-dimensional structure of said PPCA, pPPCA or at least one subdomain thereof.

10. A computer-based system according to claim 9, wherein said computer readable medium further has stored thereon data corresponding to a nucleic acid sequence or an amino acid sequence data comprising at least one structural domain or a functional domain of a PPCA or pPPCA corresponding to a portion of the amino acid sequences of Figures 13 or 14, and wherein said at least one subroutine further includes analyzing said sequence data.

11. A computer readable medium, having stored thereon atomic model data of a PPCA, pPPCA, or at least one subdomain thereof, produced by a computer system according to claim 9.

12. A method for providing an computer atomic model of a ligand of a PPCA or pPPCA, comprising

(a) providing a computer readable medium according to claim 11, having stored thereon atomic model data of a PPCA, a pPPCA or at least one subdomain thereof;

(b) providing a computer readable medium having stored thereon atomic model data sufficient to generate atomic models of potential ligands of PPCA or pPPCA;

(c) analyzing on a computer, using at least one subroutine executed in said computer, the atomic model data from (a) and the ligand data from (b), to determine binding sites of PPCA or pPPCA and to provide data output defining an atomic model of a ligand of said PPCA, pPPCA, or at least one subdomain thereof, said analyzing utilizing computing subroutines selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(d) obtaining atomic model output data defining the three-dimensional structure of a ligand of said PPCA, pPPCA or at least one subdomain thereof.

13. A computer readable medium having stored thereon the model output data produced by a method according to claim 12.

14. An isolated PPCA or pPPCA ligand, corresponding to the physical molecule of the atomic model of the ligand model produced by a method according to claim 12.

15. A computer-based system for providing an atomic model of a ligand of a PPCA or pPPCA, comprising the following elements;

(a) a computer readable medium having stored thereon atomic model data of a PPCA or pPPCA;

(b) a computer readable medium having stored thereon atomic model data sufficient to generate atomic models of potential ligands of PPCA or pPPCA;

(c) at least one computing subroutine for analyzing on a computer the atomic model data of PPCA or pPPCA from (a) and the ligand data from (b), to determine binding sites of PPCA or pPPCA and to provide data output defining a atomic models of potential ligands of PPCA or pPPCA, said analyzing utilizing at least one computing subroutine selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(d) retrieval means for obtaining atomic model output data defining the atomic models of potential ligands of PPCA or pPPCA.

16. A computer readable medium, comprising atomic model output data of a potential ligand of PPCA or pPPCA, said data produced by a method according to claim 15.

17. An isolated PPCA or pPPCA ligand, corresponding to the physical molecule of the atomic model of a ligand produced by a computer system according to claim 15.

18. A crystallized pPPCA, having the atomic coordinates presented in Figure 23.1-23.41.

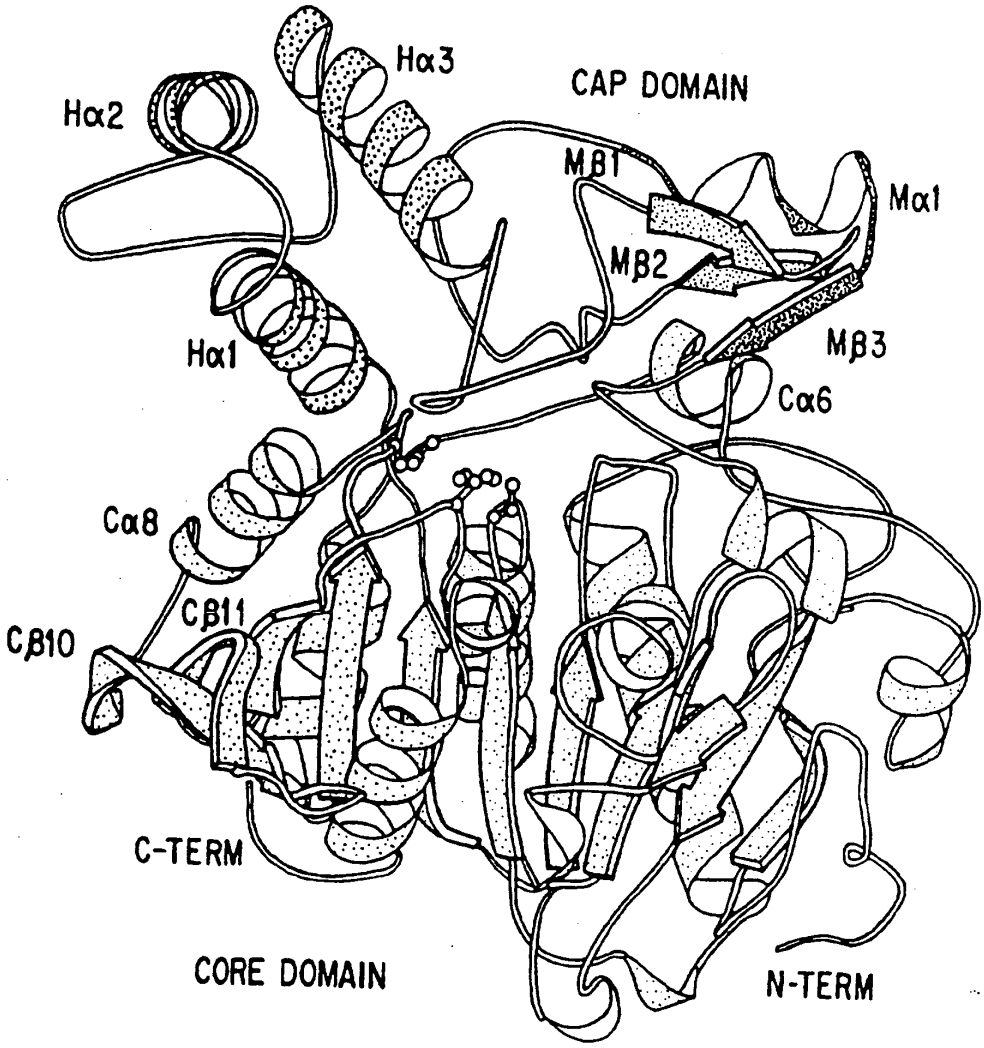

Hα3
CAP DOMAIN
Hα2
Mβ1
Mα1
Mβ2
Hα1
Mβ3
Cα6
Cα8
Cβ11
Cβ10
C-TERM
CORE DOMAIN
N-TERM

FIG. 1

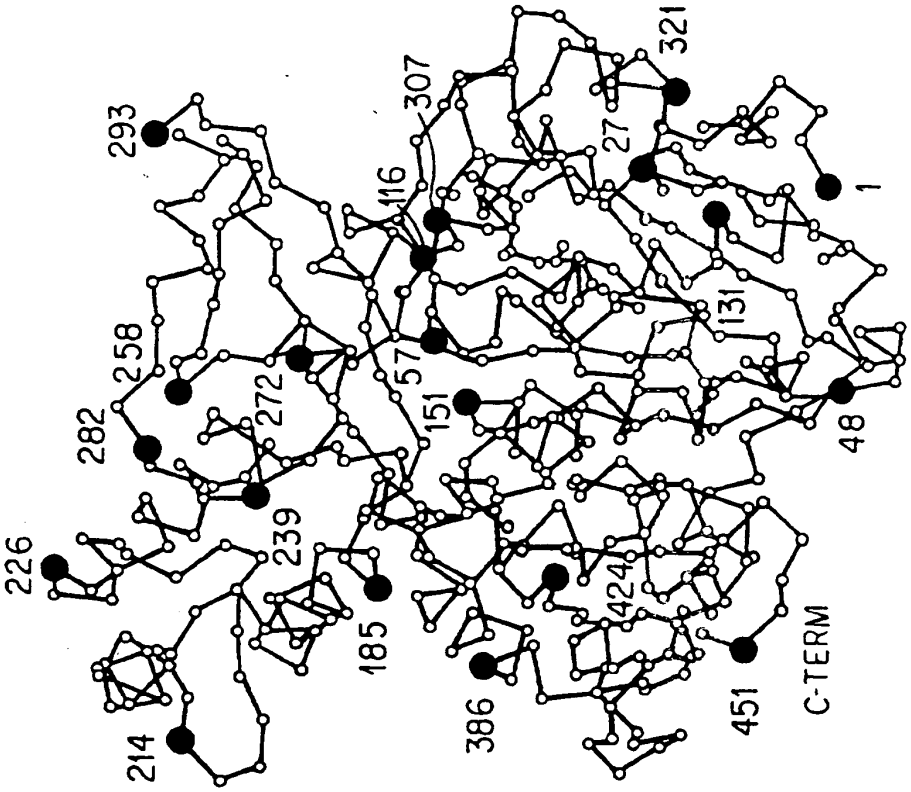

293
307
321
27
1
N-TERM
116
131
258
57
272
151
48
282
226
239
424
185
386
451
C-TERM
214

FIG.2B

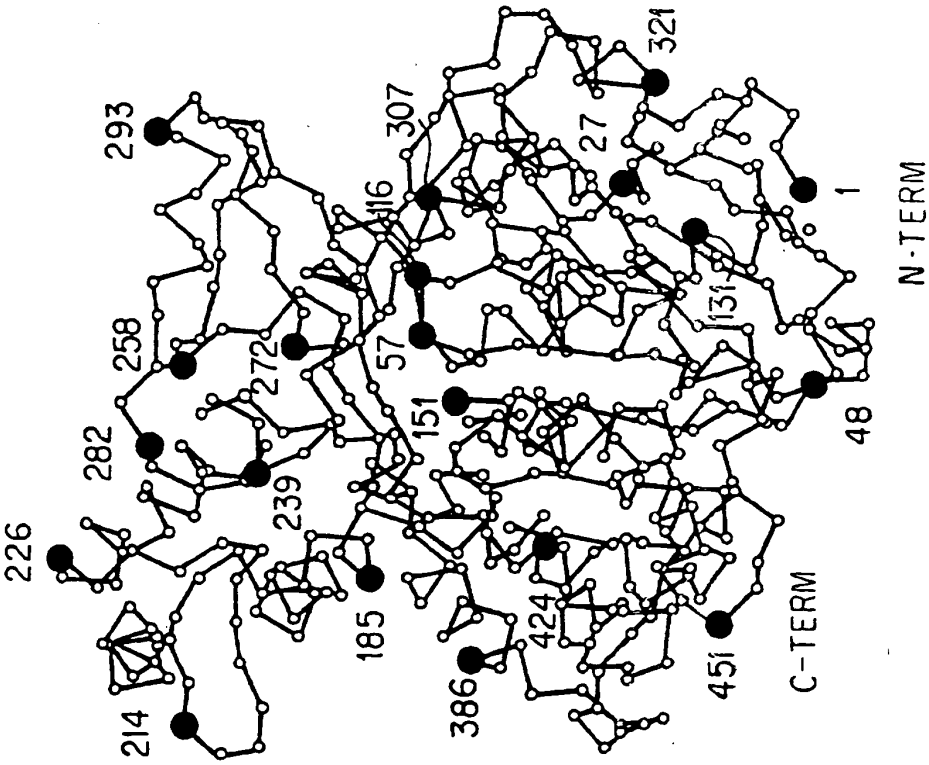

293
307
321
27
1
N-TERM
116
131
258
57
272
151
48
282
226
239
424
185
386
451
C-TERM
214

FIG.2A

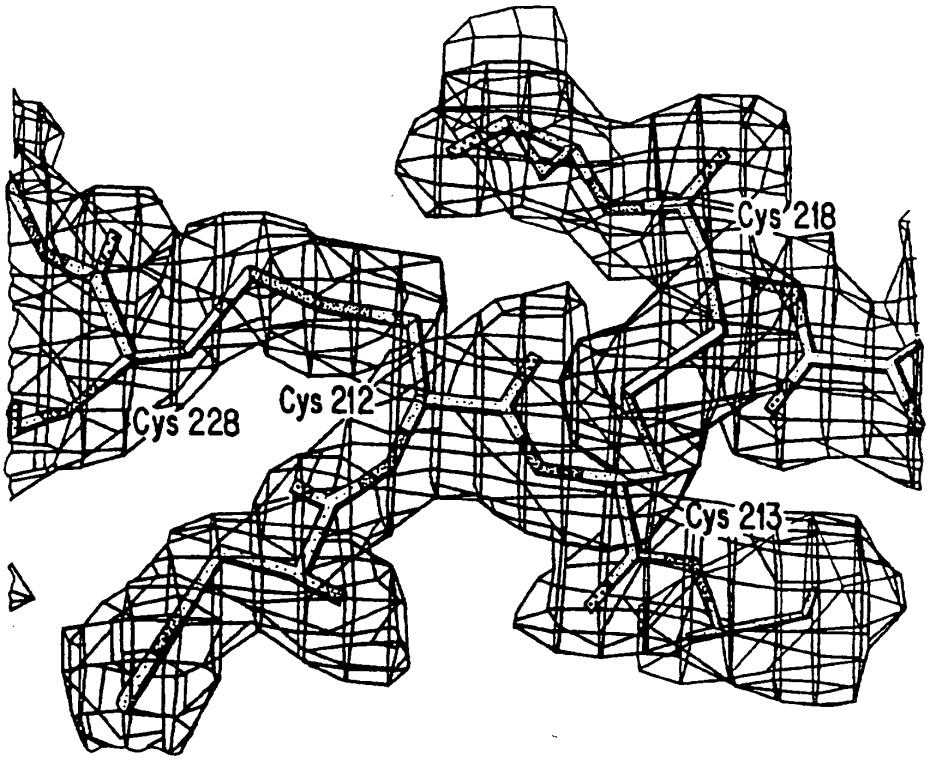


FIG. 3

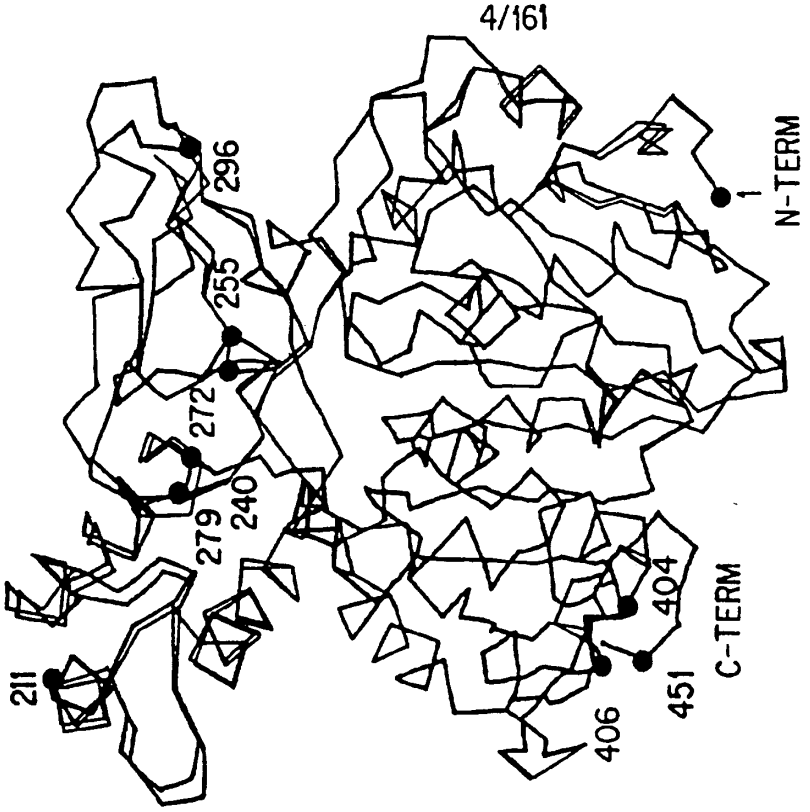

296
255
272
240
279
211
1
N-TERM
404
C-TERM
451
406

FIG. 4B

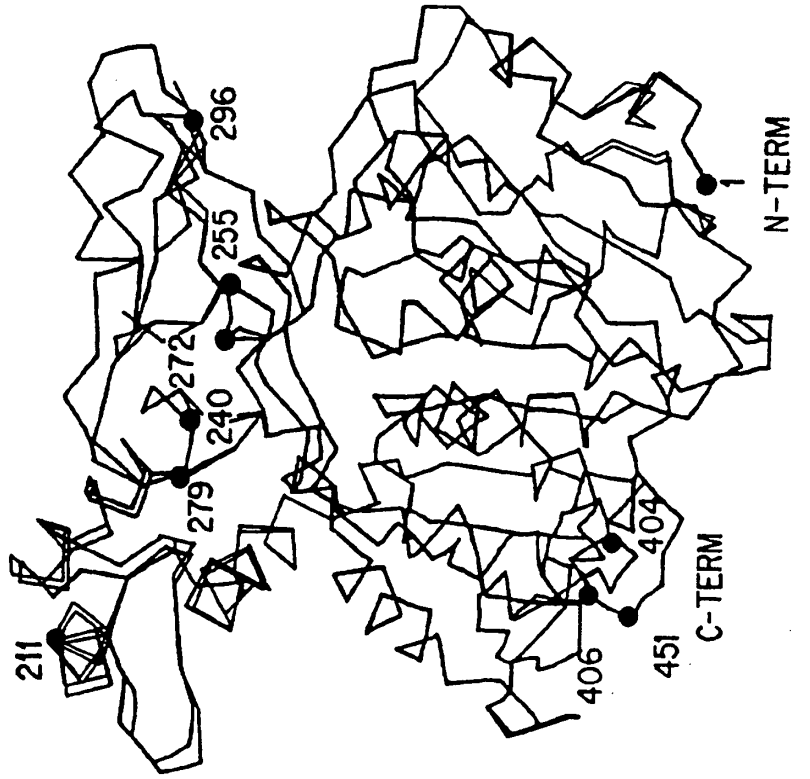

296
255
272
240
279
211
1
N-TERM
404
C-TERM
451
406

FIG. 4A

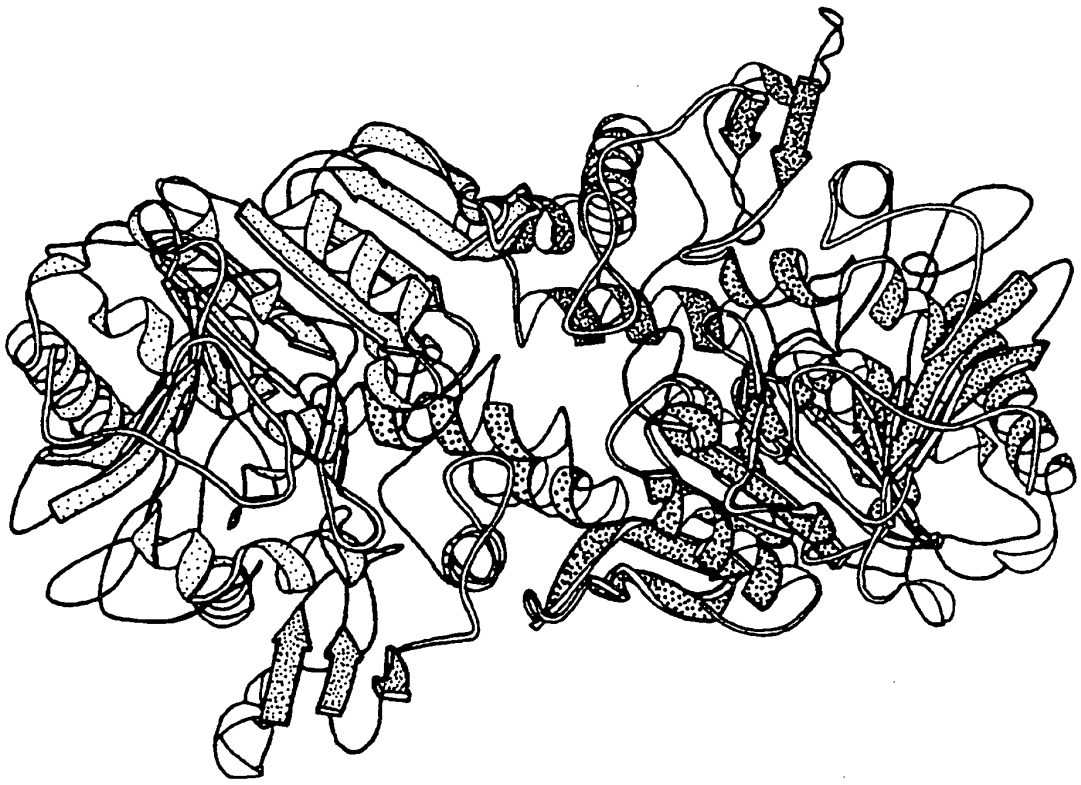


FIG. 5

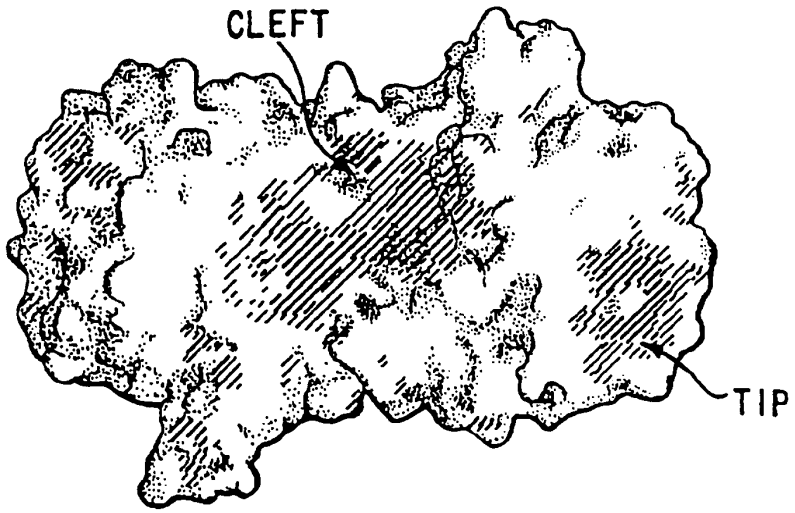


FIG. 6A

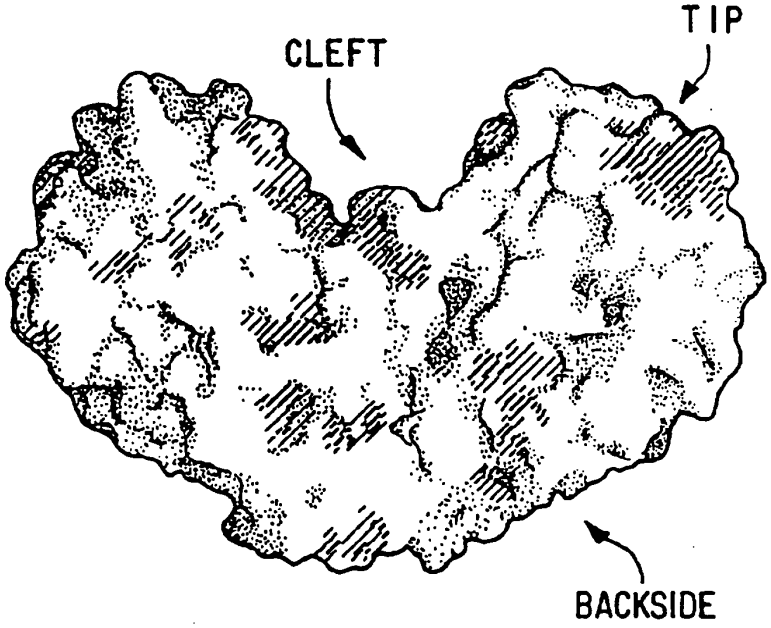


FIG. 6B

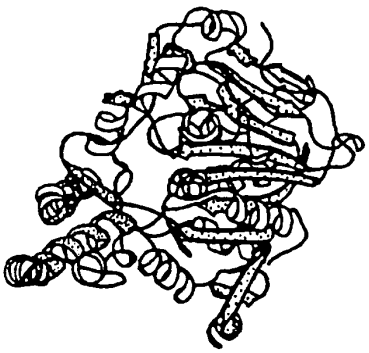


FIG.7C

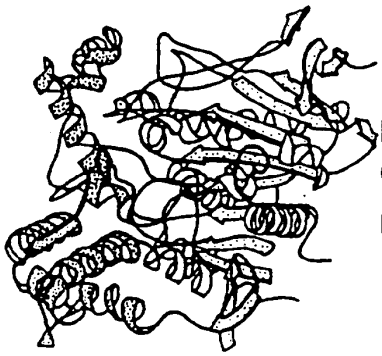


FIG.7F

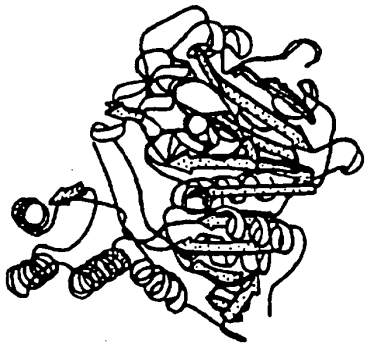


FIG.7B

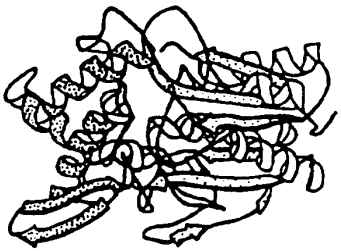


FIG.7E

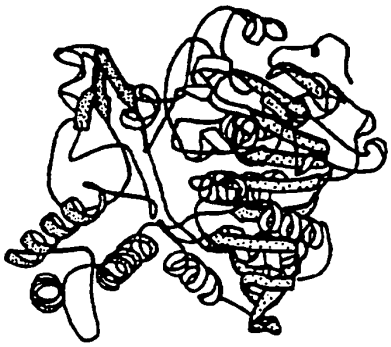


FIG.7A

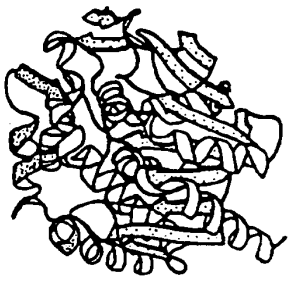


FIG.7D

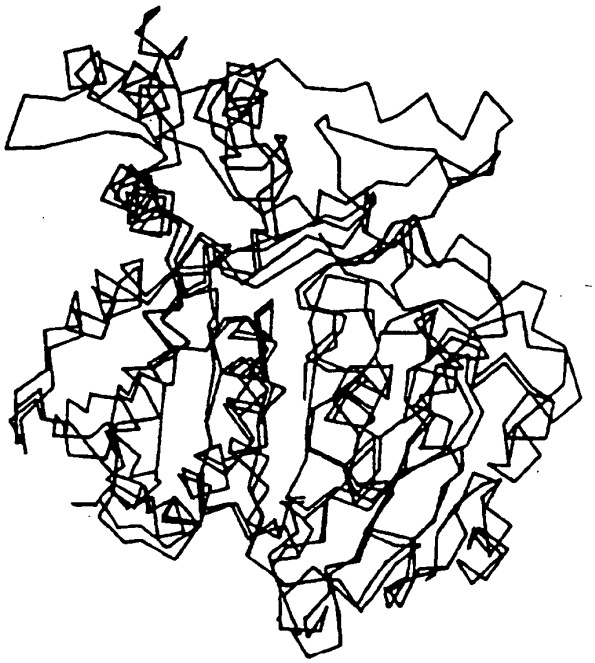


FIG. 8A

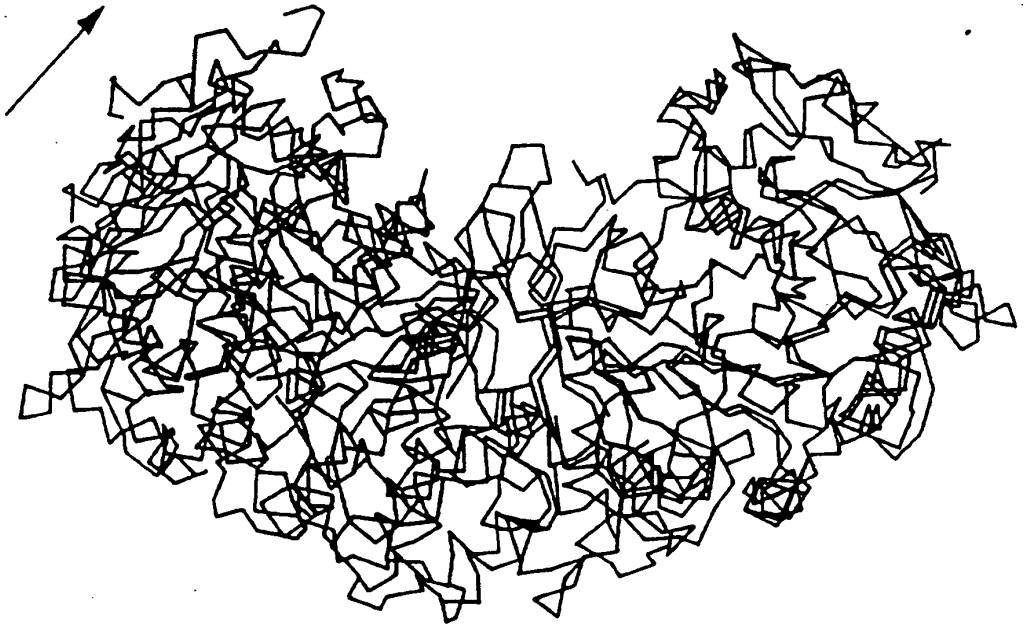


FIG. 8B

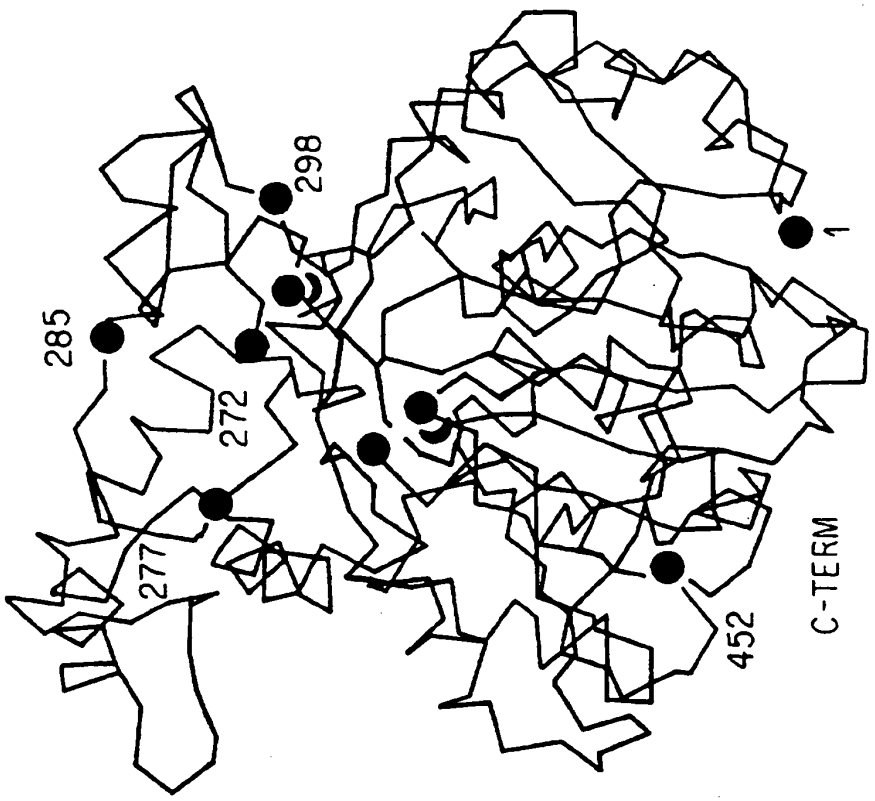

298
285
272
277
1
N-TERM
C-TERM
452

FIG.9B

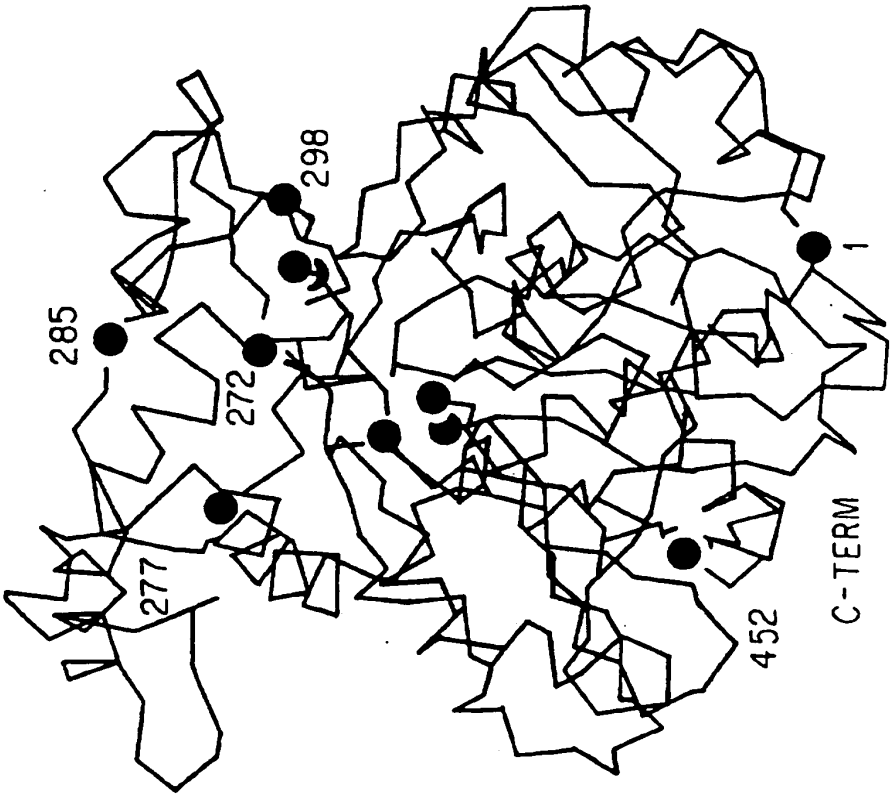

298
285
272
277
1
N-TERM
C-TERM
452

FIG.9A

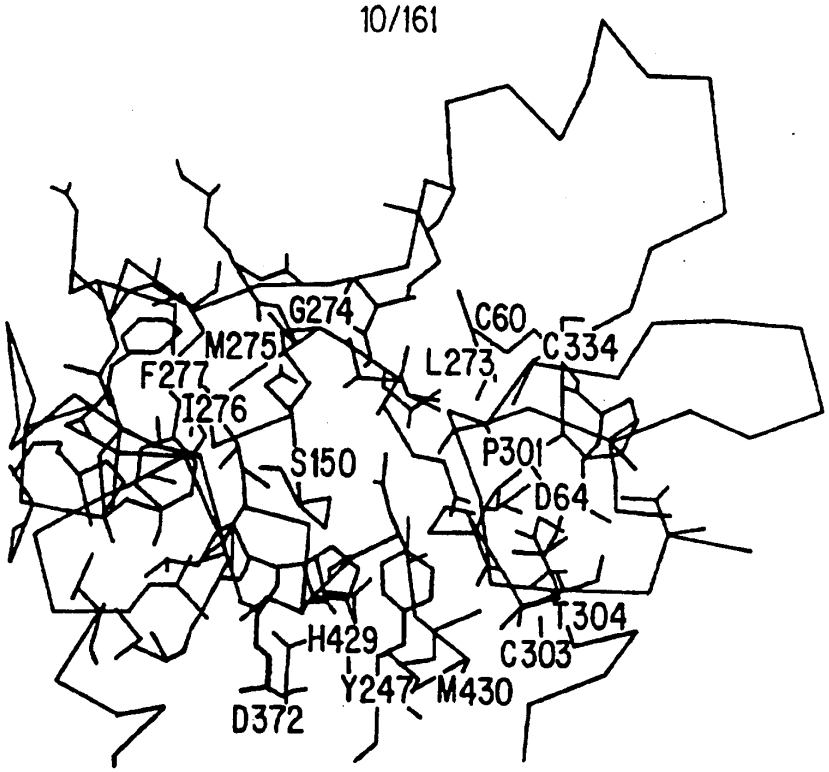


FIG. 10A

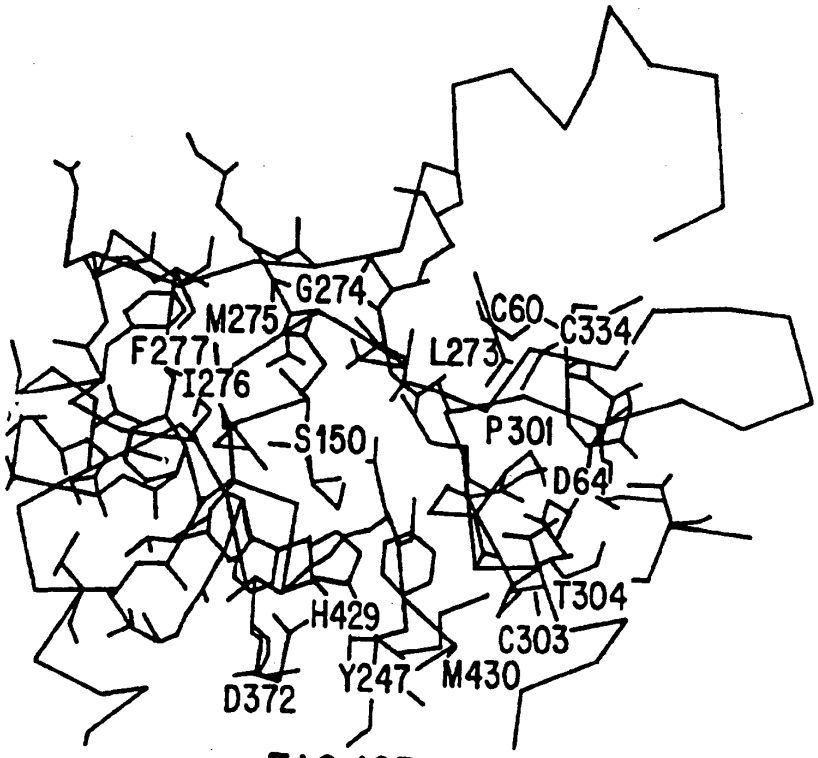


FIG. 10B

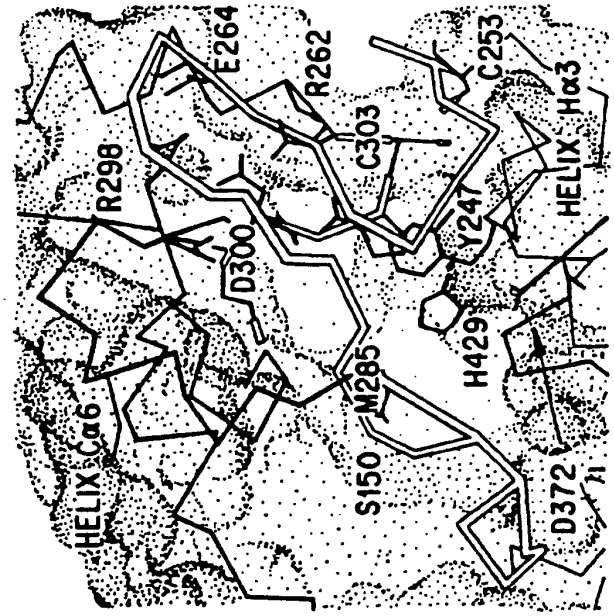


FIG.11B

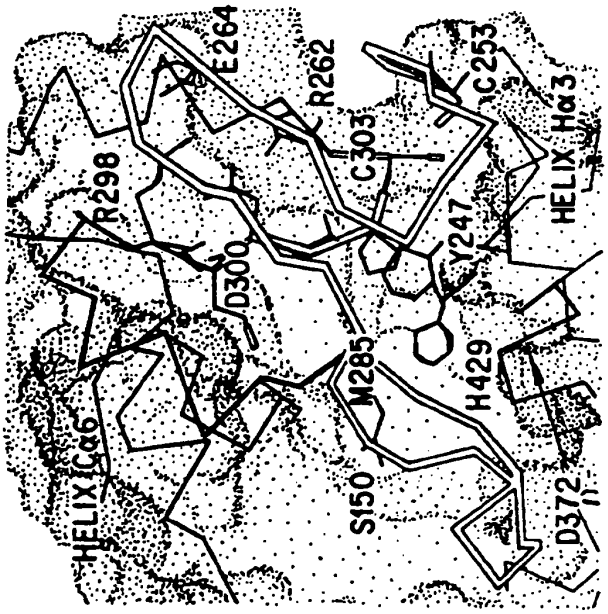


FIG.11A

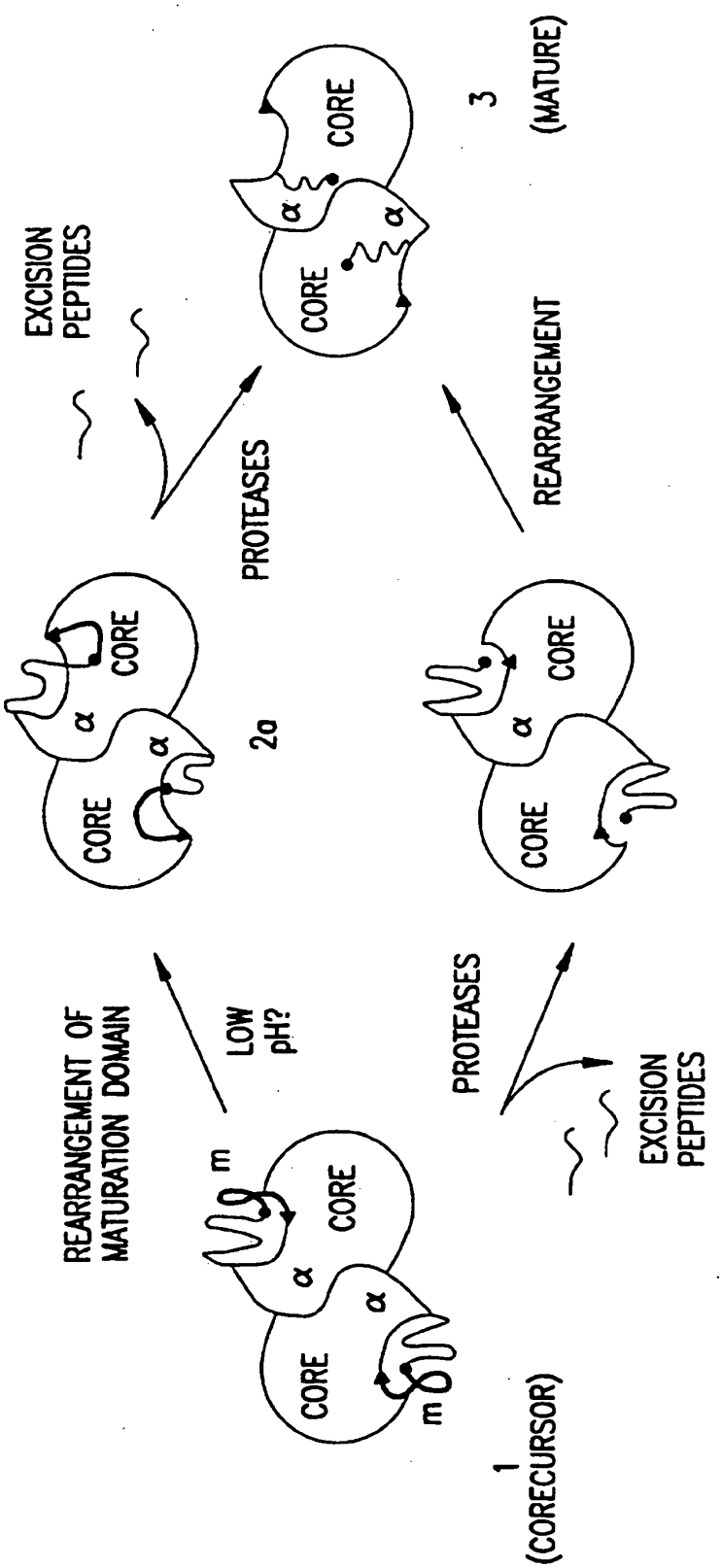

1
(CORECURSOR)
m
m
α
α
CORE
CORE
REARRANGEMENT OF
MATURATION DOMAIN
LOW
pH?
2a
2b
PROTEASES
EXCISION
PEPTIDES
EXCISION
PEPTIDES
PROTEASES
REARRANGEMENT
3
(MATURE)

FIG.12

1 A P D Q D E I Q R L P G L A K Q P S F R Q Y S G Y L K S S G

31 S K H L H Y W F V E S Q K D P E N S P V V L W L N G G P G C

61 S S L D G L L T E H G P F L V Q P D G V T L E Y N P Y S W N

91 L I A N V L Y L E S P A G V G F S Y S D D K F Y A T N D T E

121 V A Q S N F E A L Q D F F R L F P E Y K N N K L F L T G E S

151 Y A G I Y I P T L A V L V M Q D P S M N L Q G L A V G N G L

181 S S Y E Q N D N S L V Y F A Y Y H G L L G N R L W S S L Q T

211 H C C S Q N K C N F Y D N K D L E C V T N L Q E V A R I V G

241 N S G L N I Y N L Y A P C A G G V P S H F R Y E K D T V V V

271 Q D L G N I F T R L P L K R M W H Q A L L R S G D K V R M D

301 P P C T N T T A A S T Y L N N P Y V R K A L N I P E Q L P Q

331 W D M C N F L V N L Q Y R R L Y R S M N S Q Y L K L L S S Q

361 K Y Q I L L Y N G D V D M A C N F M G D E W F V D S L N Q K

391 M E V Q R R P W L V K Y G D S G E Q I A G F V K E F S H I A

421 F L T I K G A G H M V P T D K P L A A F T M F S R F L N K Q

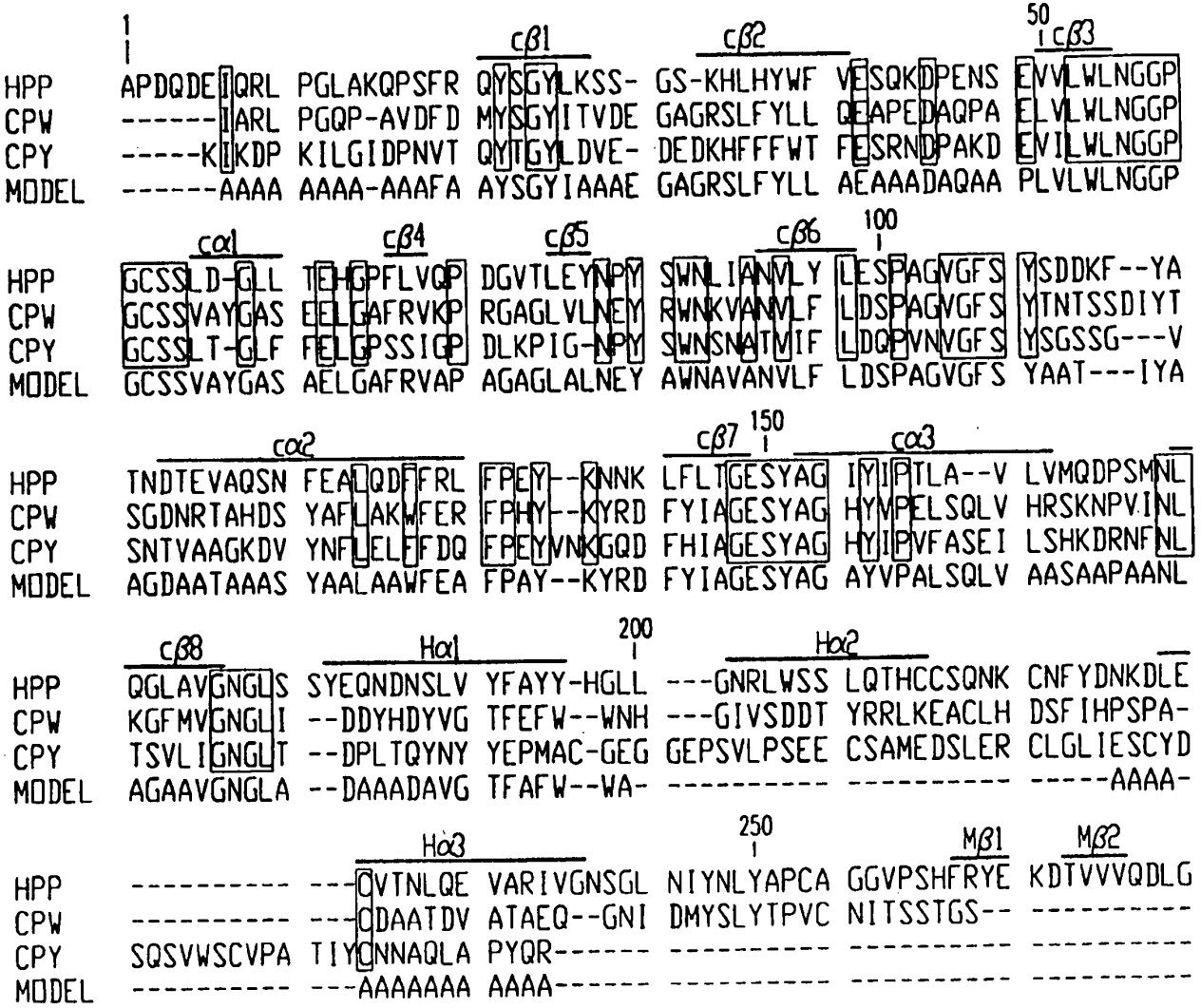
451 P Y 452

FIG.13

```
1    A P D Q D E I Q R L P G L A K Q P S F R Q Y S G Y L K S S G
31   S K H L H Y W F V E S Q K D P E N S P V V L W L N G G P G C
61   S S L D G L L T E H G P F L V Q P D G V T L E Y N P Y S W N
91   L I A N V L Y L E S P A G V G F S Y S D D K F Y A T N D T E
121  V A Q S N F E A L Q D F F R L F P E Y K N N K L F L T G E S
151  Y A G I Y I P T L A V L V M Q D P S M N L Q G L A V G N G L
181  S S Y E Q N D N S L V Y F A Y Y H G L L G N R L W S S L Q T
211  H C C S Q N K C N F Y D N K D L E C V T N L Q E V A R I V G
241  N S G L N I Y N L Y A P C A G G V P S H F R Y E K D T V V V
271  Q D L G N I F T R L P L K R M D P P C T N T T A A S T Y L N
301  N P Y V R K A L N I P E Q L P Q W D M C N F L V N L Q Y R R
331  L Y R S M N S Q Y L K L L S S Q K Y Q I L L Y N G D V D M A
361  C N F M G D E W F V D S L N Q K M E V Q R R P W L V K Y G D
391  S G E Q I A G F V K E F S H I A F L T I K G A G H M V P T D
421  K P L A A F T M F S R F L N K Q P Y                    438
```

FIG.14

FIG.15A



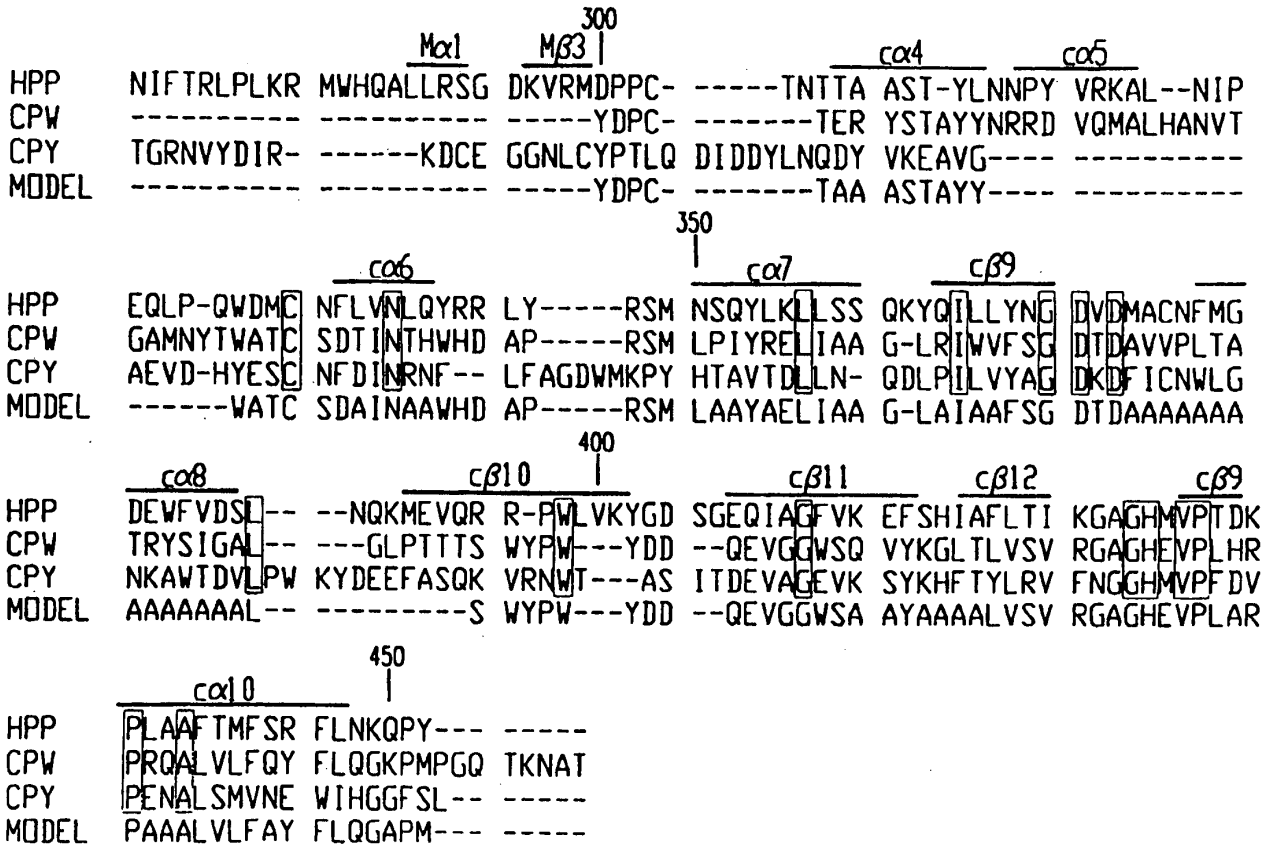


FIG.15B

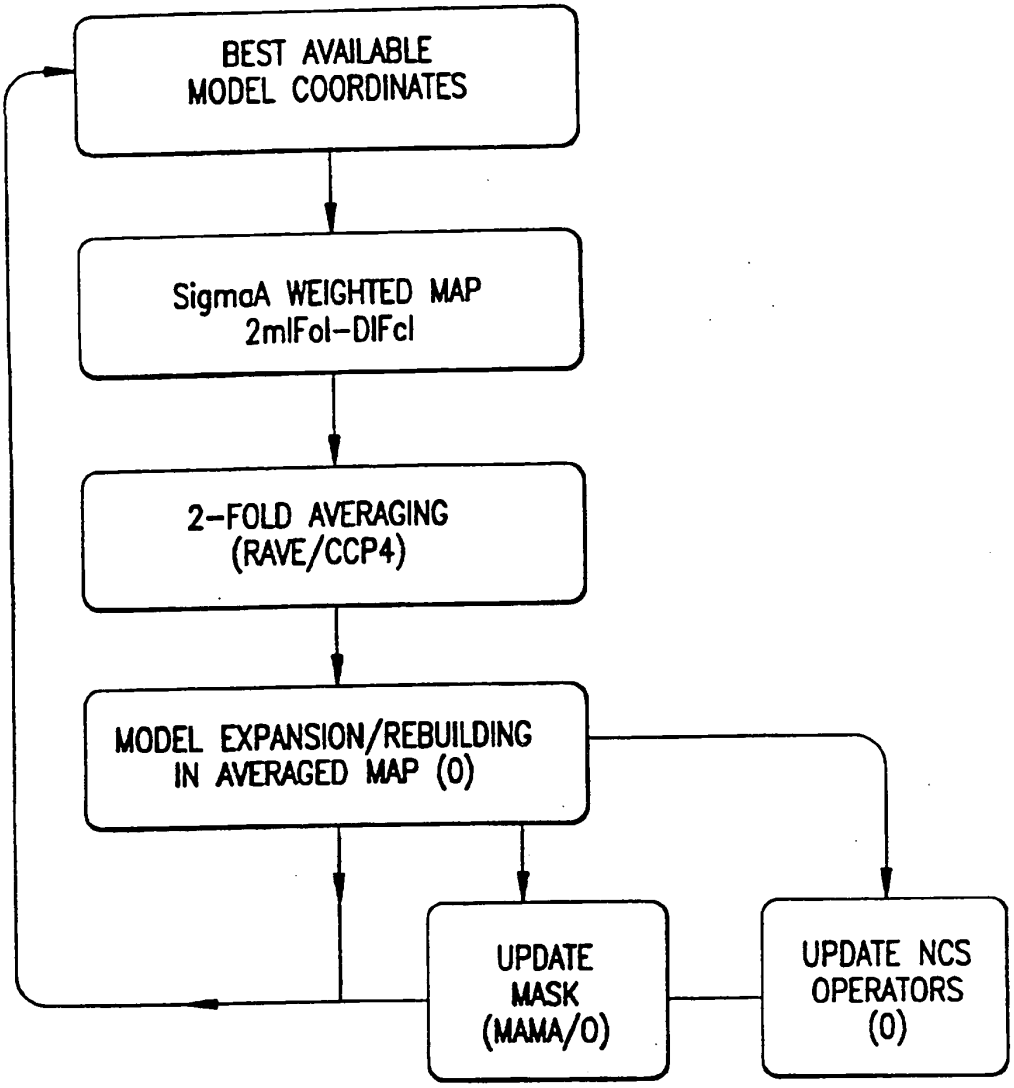

BEST AVAILABLE
MODEL COORDINATES
SigmaA WEIGHTED MAP
2mIFoI-DIFcI
2-FOLD AVERAGING
(RAVE/CCP4)
MODEL EXPANSION/REBUILDING
IN AVERAGED MAP (O)
UPDATE
MASK
(MAMA/O)
UPDATE NCS
OPERATORS
(O)

FIG.16

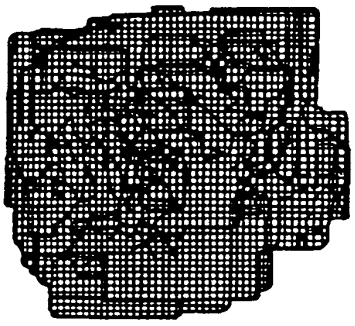


FIG. 17B

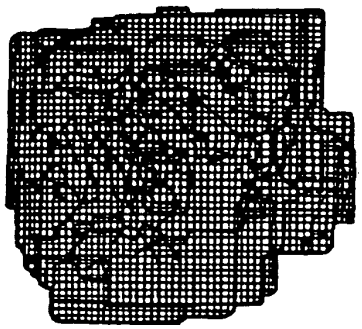


FIG. 17A

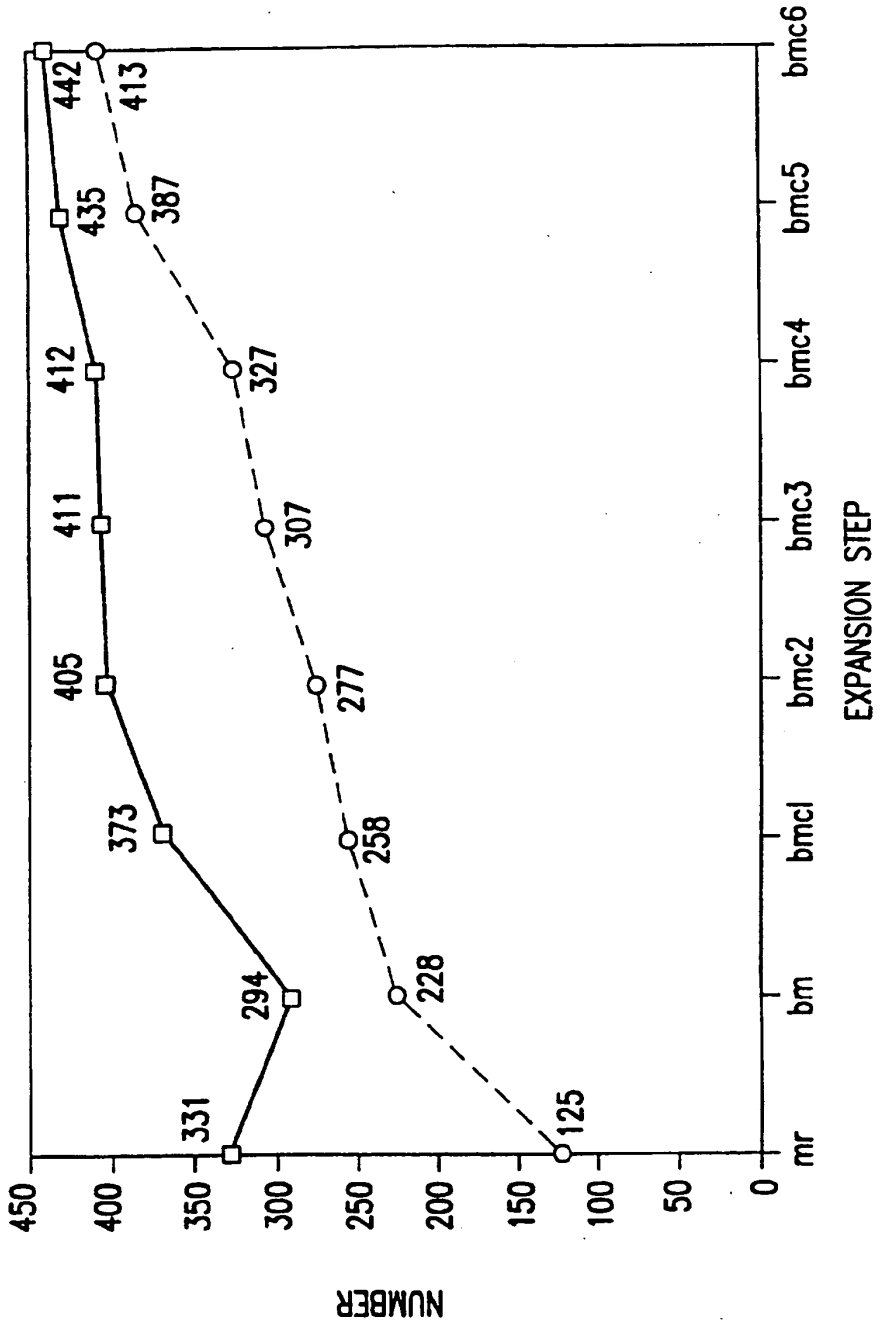

NUMBER
EXPANSION STEP
450
400
350
300
250
200
150
100
50
0
mr
bm
bmcl
bmc2
bmc3
bmc4
bmc5
bmc6
442
435
412
411
405
373
331
294
413
387
327
307
277
258
228
125

FIG.18

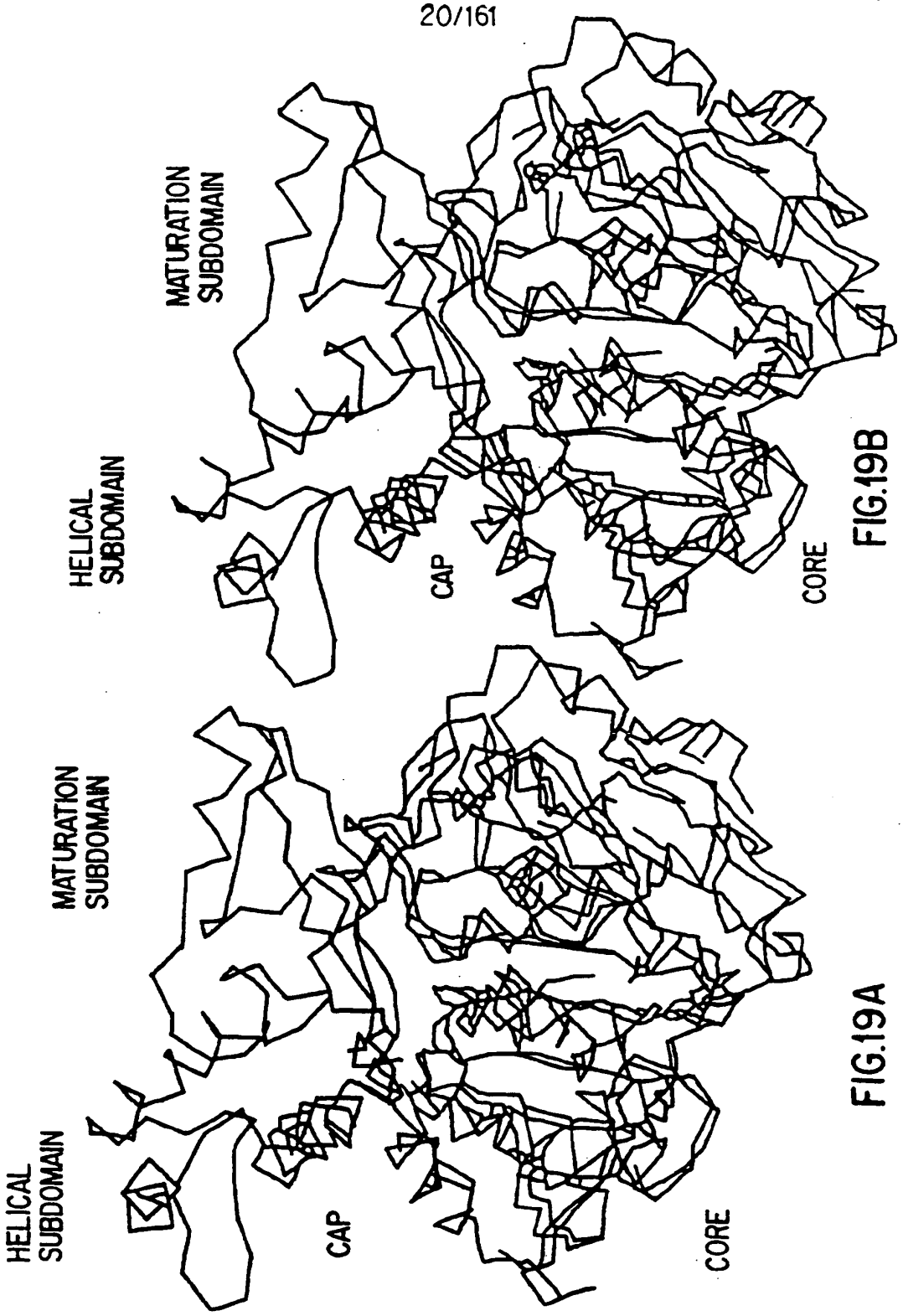


FIG.19B

FIG.19A

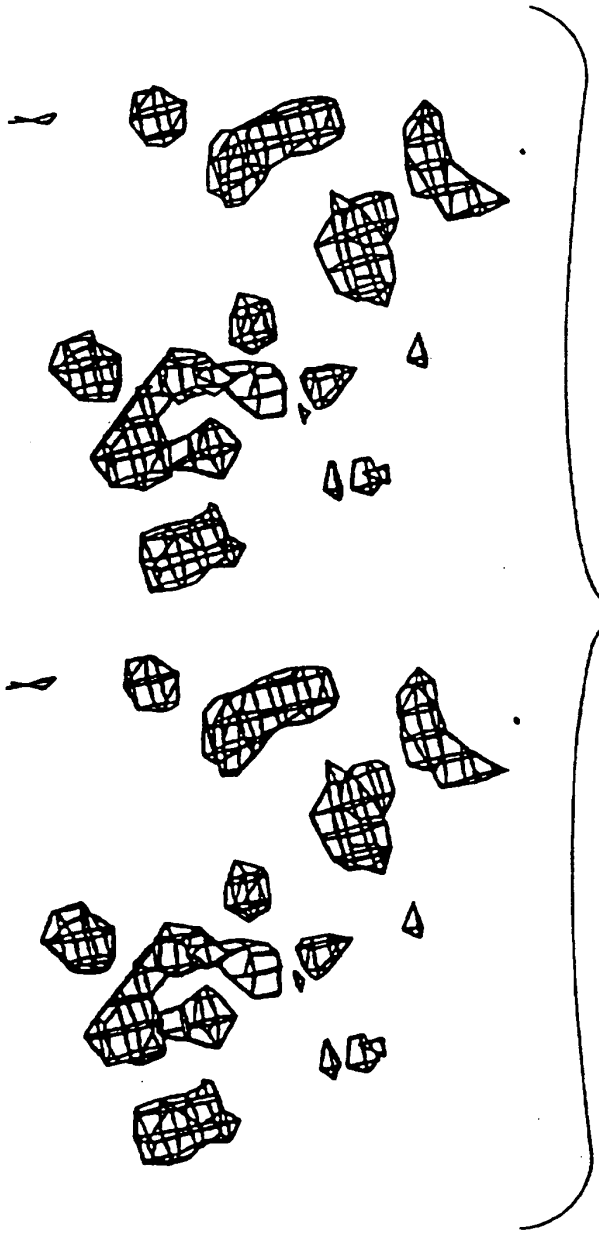


FIG. 20A

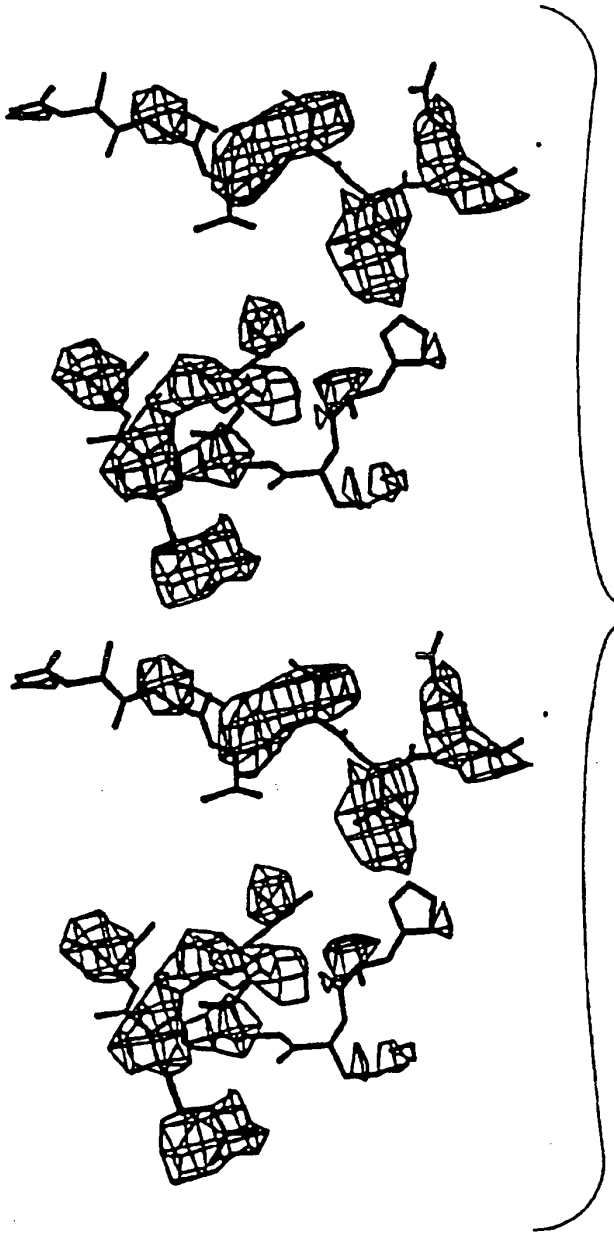


FIG. 20B

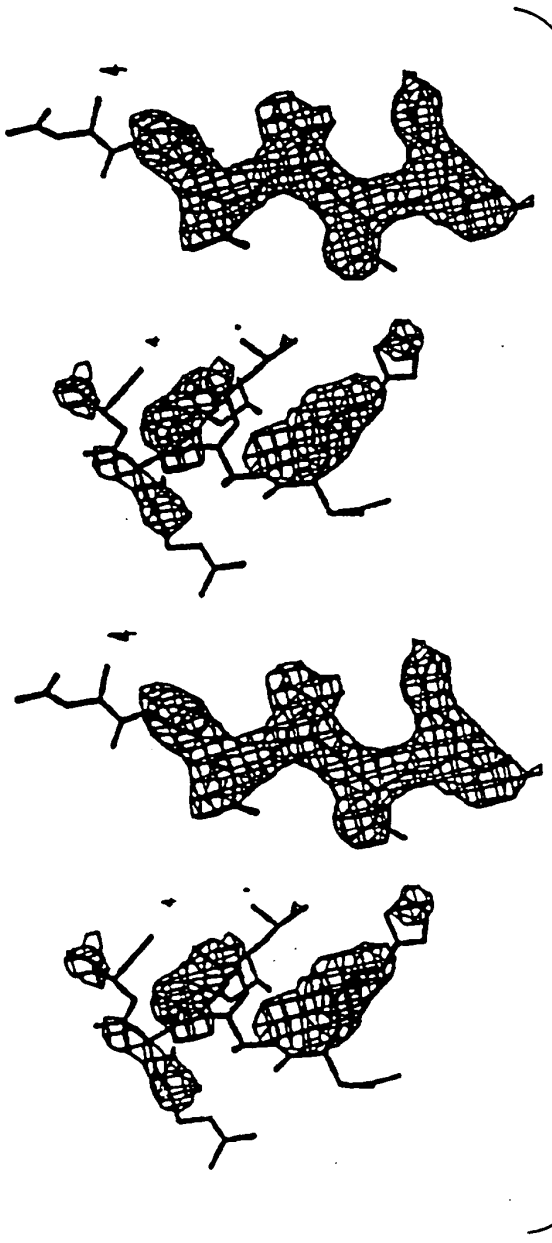


FIG. 20C

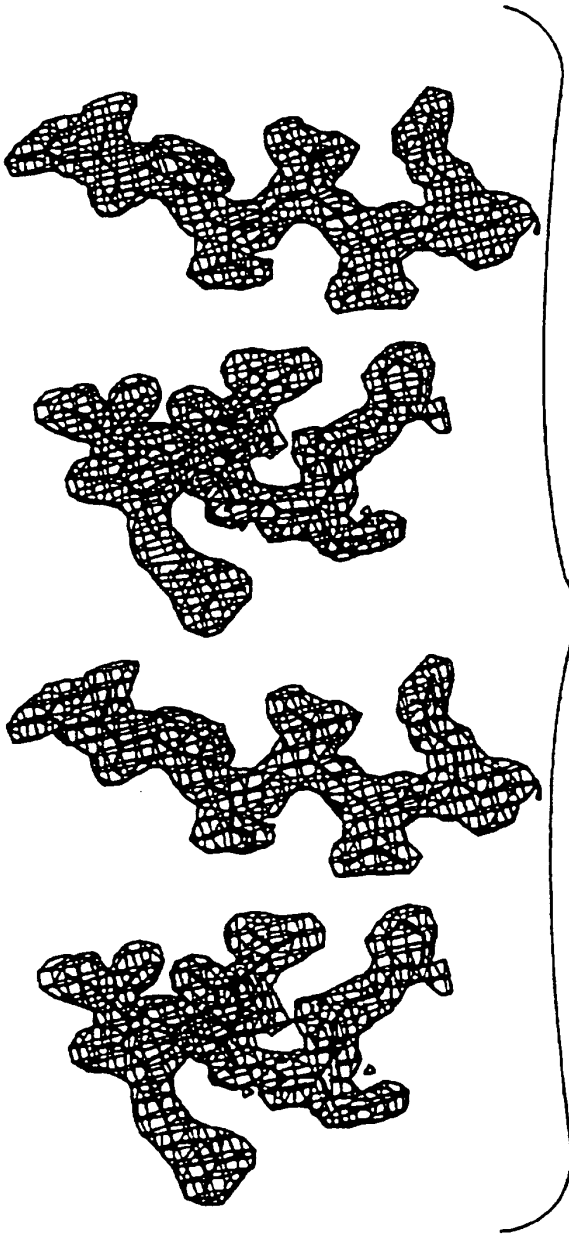


FIG. 20D

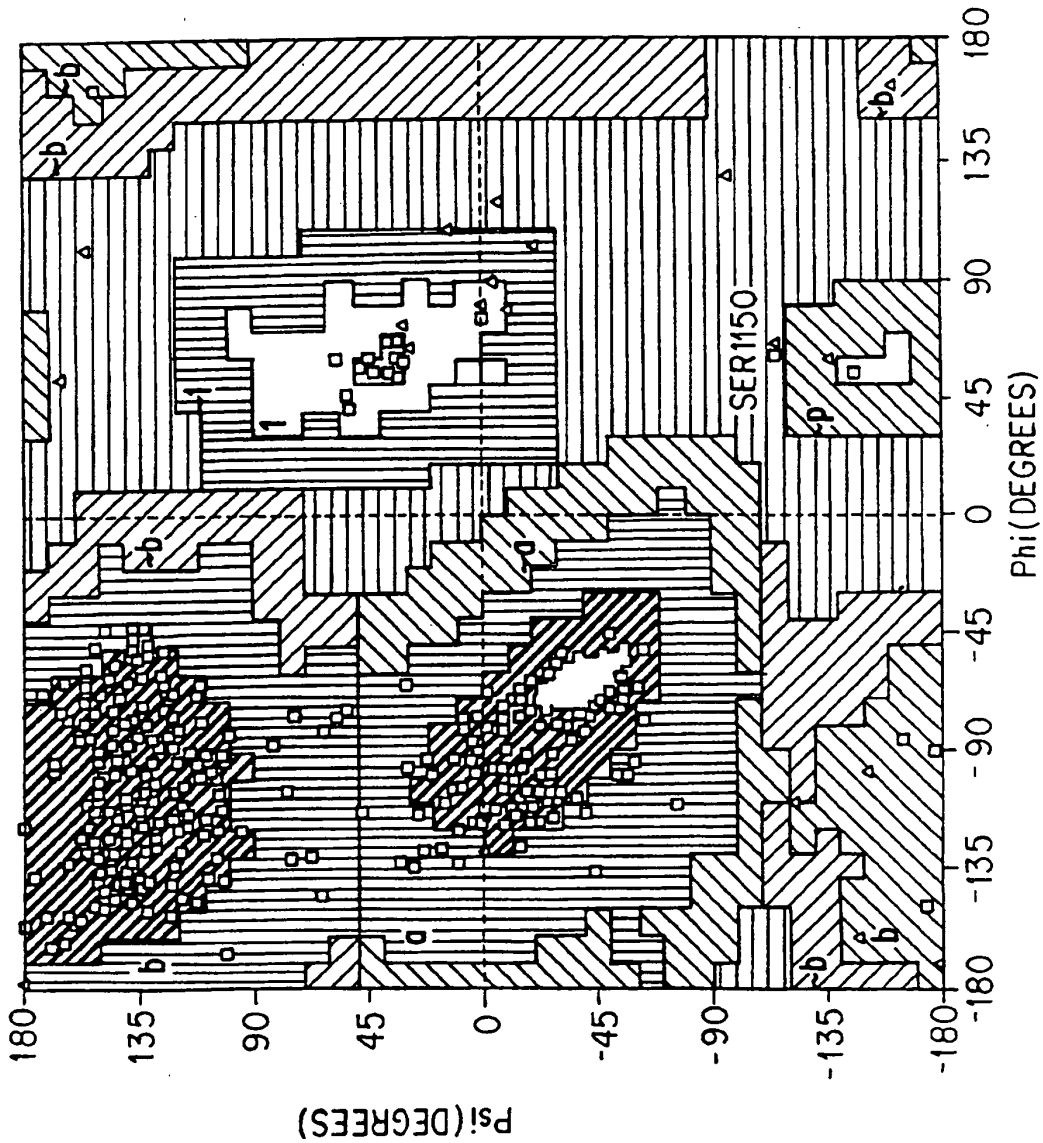


FIG.21

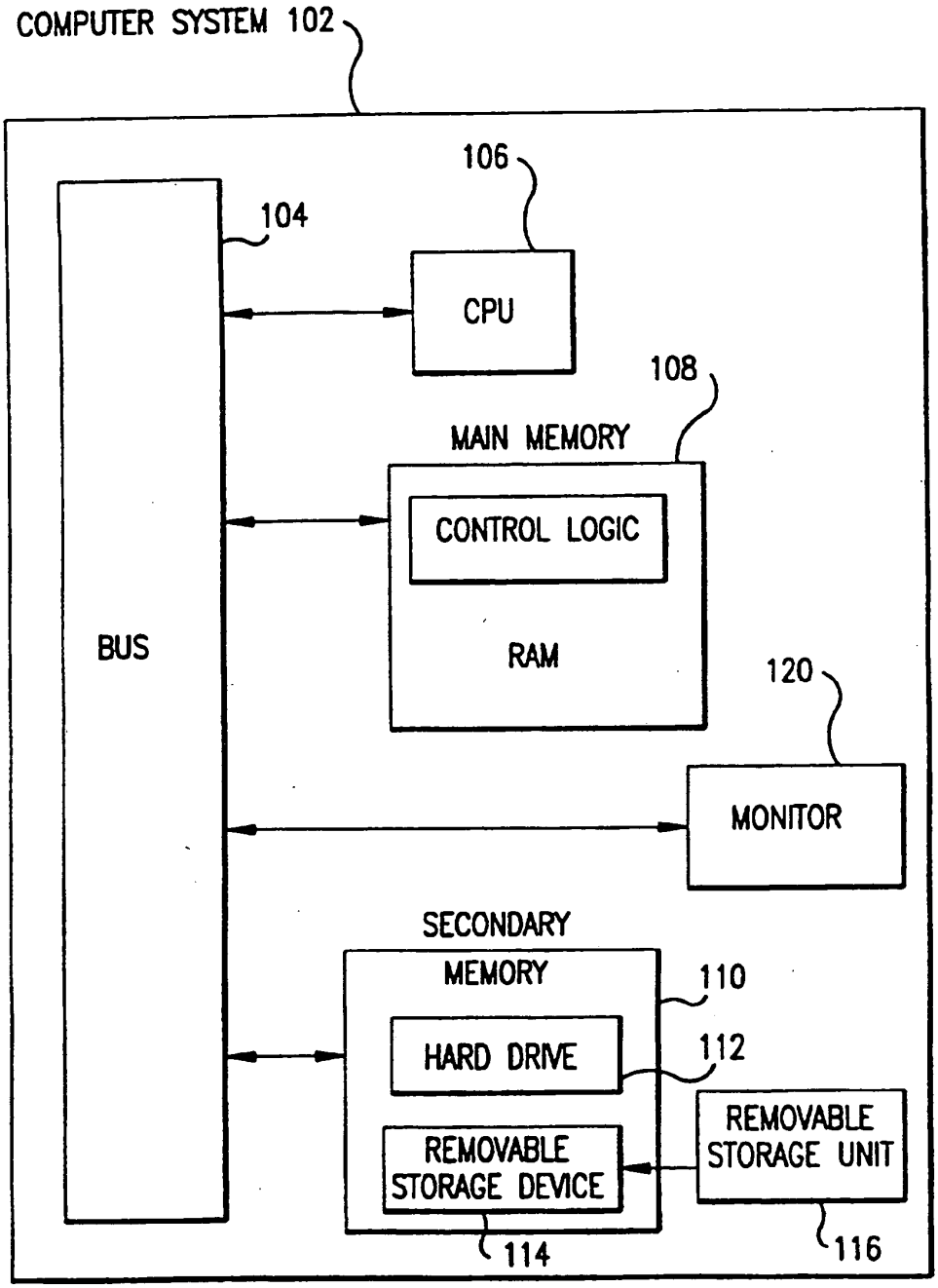

COMPUTER SYSTEM 102
106
104
CPU
108
MAIN MEMORY
CONTROL LOGIC
RAM
BUS
120
MONITOR
SECONDARY
MEMORY
110
HARD DRIVE
112
REMOVABLE
STORAGE DEVICE
REMOVABLE
STORAGE UNIT
114
116

FIG.22

```
CRYST1  115.040  148.110   80.970  90.00  90.00  90.00
ORIGX1    1.000000  0.000000  0.000000        0.00000
ORIGX2    0.000000  1.000000  0.000000        0.00000
ORIGX3    0.000000  0.000000  1.000000        0.00000
SCALE1    0.008693  0.000000  0.000000        0.00000
SCALE2    0.000000  0.006752  0.000000        0.00000
SCALE3    0.000000  0.000000  0.012350        0.00000

ATOM    397  N   VAL    50      36.021  62.379 -18.415  0.00  0.00      7
ATOM    398  CA  VAL    50      34.640  62.776 -18.328  0.00  0.00      6
ATOM    399  CB  VAL    50      34.127  63.418 -19.657  0.00  0.00      6
ATOM    400  CG1 VAL    50      32.623  63.580 -19.614  0.00  0.00      6
ATOM    401  CG2 VAL    50      34.774  64.795 -19.867  0.00  0.00      6
ATOM    402  C   VAL    50      33.952  61.433 -18.051  0.00  0.00      6
ATOM    403  O   VAL    50      34.283  60.412 -18.670  0.00  0.00      8
ATOM    404  N   VAL    51      33.060  61.424 -17.065  0.00  0.00      7
ATOM    405  CA  VAL    51      32.359  60.222 -16.675  0.00  0.00      6
ATOM    406  CB  VAL    51      32.821  59.761 -15.257  0.00  0.00      6
ATOM    407  CG1 VAL    51      31.931  58.602 -14.740  0.00  0.00      6
ATOM    408  CG2 VAL    51      34.290  59.373 -15.279  0.00  0.00      6
ATOM    409  C   VAL    51      30.872  60.478 -16.627  0.00  0.00      6
ATOM    410  O   VAL    51      30.415  61.272 -15.813  0.00  0.00      8
ATOM    411  N   LEU    52      30.117  59.815 -17.495  0.00  0.00      7
```

FIG.23.1

ATOM	412	CA	LEU	52	28.681	59.977	-17.479	0.00	0.00	6
ATOM	413	CB	LEU	52	28.082	59.634	-18.851	0.00	0.00	6
ATOM	414	CG	LEU	52	26.550	59.580	-18.920	0.00	0.00	6
ATOM	415	CD1	LEU	52	25.924	60.988	-18.820	0.00	0.00	6
ATOM	416	CD2	LEU	52	26.109	58.909	-20.219	0.00	0.00	6
ATOM	417	C	LEU	52	28.138	59.001	-16.441	0.00	0.00	6
ATOM	418	O	LEU	52	28.624	57.886	-16.346	0.00	0.00	8
ATOM	419	N	TRP	53	27.168	59.435	-15.647	0.00	0.00	7
ATOM	420	CA	TRP	53	26.546	58.567	-14.684	0.00	0.00	6
ATOM	421	CB	TRP	53	26.859	58.963	-13.230	0.00	0.00	6
ATOM	422	CG	TRP	53	26.038	58.120	-12.241	0.00	0.00	6
ATOM	423	CD2	TRP	53	26.338	56.786	-11.787	0.00	0.00	6
ATOM	424	CE2	TRP	53	25.273	56.374	-10.949	0.00	0.00	6
ATOM	425	CE3	TRP	53	27.407	55.903	-12.007	0.00	0.00	6
ATOM	426	CD1	TRP	53	24.834	58.443	-11.682	0.00	0.00	6
ATOM	427	NE1	TRP	53	24.370	57.399	-10.903	0.00	0.00	7
ATOM	428	CZ2	TRP	53	25.244	55.114	-10.326	0.00	0.00	6
ATOM	429	CZ3	TRP	53	27.380	54.644	-11.392	0.00	0.00	6
ATOM	430	CH2	TRP	53	26.306	54.266	-10.559	0.00	0.00	6
ATOM	431	C	TRP	53	25.046	58.570	-14.920	0.00	0.00	6
ATOM	432	O	TRP	53	24.413	59.626	-14.979	0.00	0.00	8
ATOM	433	N	LEU	54	24.479	57.387	-15.115	0.00	0.00	7
ATOM	434	CA	LEU	54	23.041	57.273	-15.306	0.00	0.00	6

FIG.23.2

ATOM	435	CB	LEU	54	22.708	56.740	-16.702	0.00	0.00	6
ATOM	436	CG	LEU	54	23.032	57.566	-17.936	0.00	0.00	6
ATOM	437	CD1	LEU	54	22.685	56.668	-19.137	0.00	0.00	6
ATOM	438	CD2	LEU	54	22.223	58.891	-17.958	0.00	0.00	6
ATOM	439	C	LEU	54	22.486	56.281	-14.317	0.00	0.00	6
ATOM	440	O	LEU	54	23.071	55.226	-14.108	0.00	0.00	8
ATOM	441	N	ASN	55	21.351	56.608	-13.726	0.00	0.00	7
ATOM	442	CA	ASN	55	20.688	55.725	-12.793	0.00	0.00	6
ATOM	443	CB	ASN	55	20.032	56.536	-11.652	0.00	0.00	6
ATOM	444	CG	ASN	55	20.936	56.660	-10.429	0.00	0.00	6
ATOM	445	OD1	ASN	55	21.657	57.646	-10.237	0.00	0.00	8
ATOM	446	ND2	ASN	55	20.933	55.631	-9.616	0.00	0.00	7
ATOM	447	C	ASN	55	19.664	54.990	-13.661	0.00	0.00	6
ATOM	448	O	ASN	55	19.648	55.169	-14.877	0.00	0.00	8
ATOM	449	N	GLY	56	18.785	54.195	-13.073	0.00	0.00	7
ATOM	450	CA	GLY	56	17.852	53.473	-13.910	0.00	0.00	6
ATOM	451	C	GLY	56	16.396	53.736	-13.709	0.00	0.00	6
ATOM	452	O	GLY	56	15.913	54.855	-13.903	0.00	0.00	8
ATOM	453	N	GLY	57	15.677	52.655	-13.421	0.00	0.00	7
ATOM	454	CA	GLY	57	14.251	52.709	-13.205	0.00	0.00	6
ATOM	455	C	GLY	57	13.593	51.518	-13.880	0.00	0.00	6
ATOM	456	O	GLY	57	13.493	50.460	-13.247	0.00	0.00	8
ATOM	457	N	PRO	58	13.172	51.628	-15.166	0.00	0.00	7

FIG.23.3

```
ATOM    458  CD  PRO    58      12.540  50.553 -15.962  0.00  0.00      6
ATOM    459  CA  PRO    58      13.304  52.837 -15.985  0.00  0.00      6
ATOM    460  CB  PRO    58      12.968  52.332 -17.402  0.00  0.00      6
ATOM    461  CG  PRO    58      11.954  51.304 -17.155  0.00  0.00      6
ATOM    462  C   PRO    58      12.358  53.953 -15.536  0.00  0.00      6
ATOM    463  O   PRO    58      11.229  53.697 -15.113  0.00  0.00      8
ATOM    464  N   GLY    59      12.868  55.178 -15.559  0.00  0.00      7
ATOM    465  CA  GLY    59      12.066  56.326 -15.176  0.00  0.00      6
ATOM    466  C   GLY    59      12.517  57.033 -13.914  0.00  0.00      6
ATOM    467  O   GLY    59      11.765  57.840 -13.410  0.00  0.00      8
ATOM    468  N   CYS    60      13.714  56.724 -13.416  0.00  0.00      7
ATOM    469  CA  CYS    60      14.250  57.331 -12.192  0.00  0.00      6
ATOM    470  C   CYS    60      15.438  58.284 -12.465  0.00  0.00      6
ATOM    471  O   CYS    60      16.164  58.149 -13.469  0.00  0.00      8
ATOM    472  CB  CYS    60      14.622  56.255 -11.136  0.00  0.00      6
ATOM    473  SG  CYS    60      13.226  55.179 -10.628  0.00  0.00     16
ATOM    474  N   SER    61      15.643  59.211 -11.535  0.00  0.00      7
ATOM    475  CA  SER    61      16.652  60.256 -11.628  0.00  0.00      6
ATOM    476  CB  SER    61      16.133  61.457 -10.818  0.00  0.00      6
ATOM    477  OG  SER    61      17.135  62.428 -10.630  0.00  0.00      8
ATOM    478  C   SER    61      18.109  59.946 -11.244  0.00  0.00      6
ATOM    479  O   SER    61      18.358  59.345 -10.207  0.00  0.00      8
ATOM    480  N   SER    62      19.057  60.441 -12.058  0.00  0.00      7
```

FIG.23.4

```
ATOM    481  CA  SER    62      20.508  60.290 -11.849  0.00  0.00      6
ATOM    482  CB  SER    62      21.302  60.634 -13.126  0.00  0.00      6
ATOM    483  OG  SER    62      21.116  59.682 -14.165  0.00  0.00      8
ATOM    484  C   SER    62      21.016  61.181 -10.719  0.00  0.00      6
ATOM    485  O   SER    62      22.177  61.100 -10.319  0.00  0.00      8
ATOM    486  N   LEU    63      20.160  62.088 -10.259  0.00  0.00      7
ATOM    487  CA  LEU    63      20.508  62.981  -9.148  0.00  0.00      6
ATOM    488  CB  LEU    63      19.515  64.138  -9.053  0.00  0.00      6
ATOM    489  CG  LEU    63      19.576  64.997 -10.303  0.00  0.00      6
ATOM    490  CD1 LEU    63      18.999  66.339  -9.936  0.00  0.00      6
ATOM    491  CD2 LEU    63      21.005  65.110 -10.828  0.00  0.00      6
ATOM    492  C   LEU    63      20.515  62.163  -7.861  0.00  0.00      6
ATOM    493  O   LEU    63      21.000  62.605  -6.819  0.00  0.00      8
ATOM    494  N   ASP    64      19.916  60.984  -7.956  0.00  0.00      7
ATOM    495  CA  ASP    64      19.874  60.008  -6.885  0.00  0.00      6
ATOM    496  CB  ASP    64      19.012  58.838  -7.335  0.00  0.00      6
ATOM    497  CG  ASP    64      18.860  57.759  -6.291  0.00  0.00      6
ATOM    498  OD1 ASP    64      19.314  57.931  -5.132  0.00  0.00      8
ATOM    499  OD2 ASP    64      18.255  56.723  -6.643  0.00  0.00      8
ATOM    500  C   ASP    64      21.332  59.592  -6.749  0.00  0.00      6
ATOM    501  O   ASP    64      21.886  59.648  -5.668  0.00  0.00      8
ATOM    502  N   GLY    65      21.992  59.287  -7.864  0.00  0.00      7
ATOM    503  CA  GLY    65      23.390  58.909  -7.792  0.00  0.00      6
```

FIG.23.5

```
ATOM    504  C   GLY  65      24.241  60.018  -7.200  0.00  0.00      6
ATOM    505  O   GLY  65      25.236  59.761  -6.526  0.00  0.00      8
ATOM    506  N   LEU  66      23.856  61.262  -7.446  0.00  0.00      7
ATOM    507  CA  LEU  66      24.602  62.427  -6.952  0.00  0.00      6
ATOM    508  CB  LEU  66      24.219  63.715  -7.736  0.00  0.00      6
ATOM    509  CG  LEU  66      25.197  64.918  -7.715  0.00  0.00      6
ATOM    510  CD1 LEU  66      24.924  65.836  -8.873  0.00  0.00      6
ATOM    511  CD2 LEU  66      25.137  65.700  -6.413  0.00  0.00      6
ATOM    512  C   LEU  66      24.384  62.665  -5.478  0.00  0.00      6
ATOM    513  O   LEU  66      25.300  62.541  -4.674  0.00  0.00      8
ATOM    514  N   LEU  67      23.151  63.002  -5.153  0.00  0.00      7
ATOM    515  CA  LEU  67      22.754  63.315  -3.792  0.00  0.00      6
ATOM    516  CB  LEU  67      21.392  64.015  -3.812  0.00  0.00      6
ATOM    517  CG  LEU  67      21.406  65.358  -4.557  0.00  0.00      6
ATOM    518  CD1 LEU  67      20.026  65.954  -4.615  0.00  0.00      6
ATOM    519  CD2 LEU  67      22.351  66.311  -3.868  0.00  0.00      6
ATOM    520  C   LEU  67      22.764  62.177  -2.773  0.00  0.00      6
ATOM    521  O   LEU  67      22.826  62.446  -1.578  0.00  0.00      8
ATOM    522  N   THR  68      22.653  60.923  -3.209  0.00  0.00      7
ATOM    523  CA  THR  68      22.644  59.833  -2.248  0.00  0.00      6
ATOM    524  CB  THR  68      21.271  59.151  -2.150  0.00  0.00      6
ATOM    525  OG1 THR  68      21.197  58.063  -3.080  0.00  0.00      8
ATOM    526  CG2 THR  68      20.141  60.138  -2.433  0.00  0.00      6
```

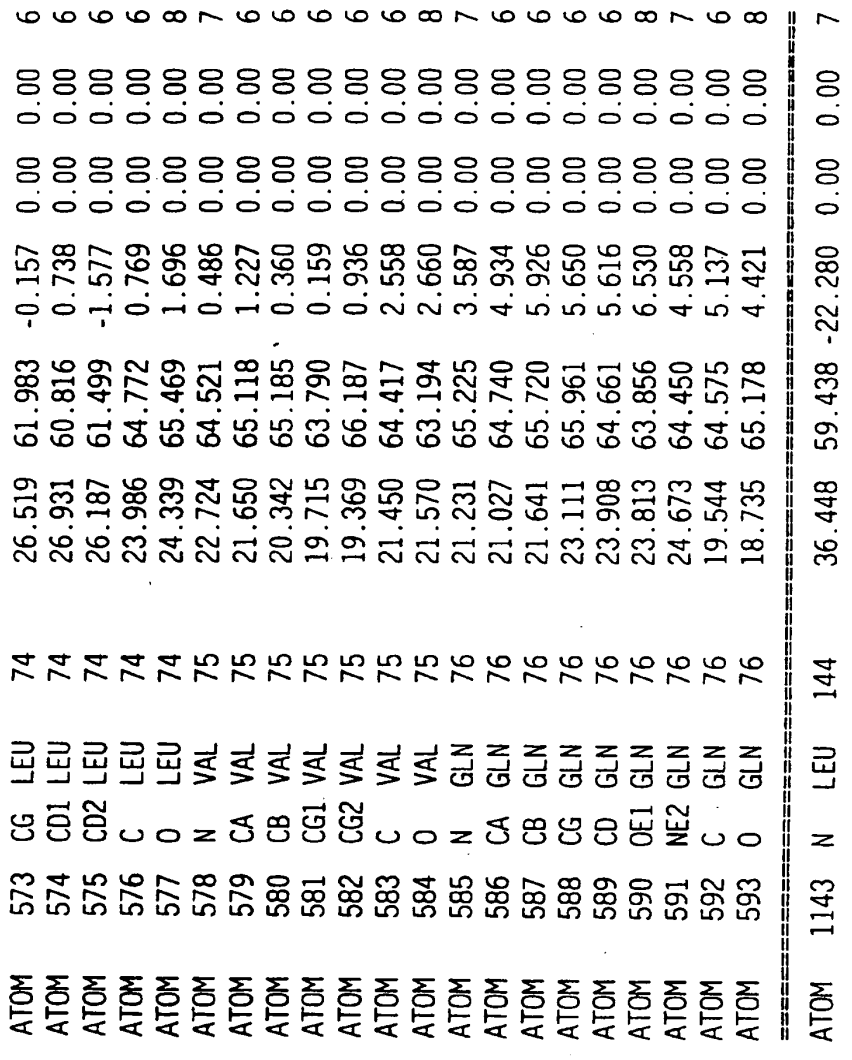
FIG.23.6

ATOM	527	C	THR	68	23.694	58.746	-2.407	0.00	0.00	6
ATOM	528	O	THR	68	23.931	57.988	-1.463	0.00	0.00	8
ATOM	529	N	GLU	69	24.357	58.707	-3.566	0.00	0.00	7
ATOM	530	CA	GLU	69	25.376	57.694	-3.853	0.00	0.00	6
ATOM	531	CB	GLU	69	25.062	56.954	-5.156	0.00	0.00	6
ATOM	532	CG	GLU	69	23.739	56.278	-5.130	0.00	0.00	6
ATOM	533	CD	GLU	69	23.517	55.370	-6.308	0.00	0.00	6
ATOM	534	OE1	GLU	69	24.108	54.278	-6.317	0.00	0.00	8
ATOM	535	OE2	GLU	69	22.731	55.733	-7.214	0.00	0.00	8
ATOM	536	C	GLU	69	26.822	58.134	-3.859	0.00	0.00	6
ATOM	537	O	GLU	69	27.568	57.843	-2.920	0.00	0.00	8
ATOM	538	N	HIS	70	27.262	58.812	-4.905	0.00	0.00	7
ATOM	539	CA	HIS	70	28.658	59.215	-4.953	0.00	0.00	6
ATOM	540	CB	HIS	70	29.455	58.238	-5.816	0.00	0.00	6
ATOM	541	CG	HIS	70	28.876	58.067	-7.185	0.00	0.00	6
ATOM	542	CD2	HIS	70	28.346	58.969	-8.044	0.00	0.00	6
ATOM	543	ND1	HIS	70	28.747	56.832	-7.792	0.00	0.00	7
ATOM	544	CE1	HIS	70	28.147	56.986	-8.960	0.00	0.00	6
ATOM	545	NE2	HIS	70	27.894	58.272	-9.135	0.00	0.00	7
ATOM	546	C	HIS	70	28.927	60.640	-5.424	0.00	0.00	6
ATOM	547	O	HIS	70	29.979	60.890	-6.024	0.00	0.00	8
ATOM	548	N	GLY	71	27.965	61.535	-5.192	0.00	0.00	7
ATOM	549	CA	GLY	71	28.122	62.937	-5.556	0.00	0.00	6

FIG.23.7

ATOM	550	C	GLY	71	29.095	63.607	-4.605	0.00	0.00	6
ATOM	551	O	GLY	71	29.423	63.023	-3.560	0.00	0.00	8
ATOM	552	N	PRO	72	29.589	64.815	-4.916	0.00	0.00	7
ATOM	553	CD	PRO	72	29.328	65.626	-6.110	0.00	0.00	6
ATOM	554	CA	PRO	72	30.543	65.490	-4.024	0.00	0.00	6
ATOM	555	CB	PRO	72	30.948	66.730	-4.831	0.00	0.00	6
ATOM	556	CG	PRO	72	29.757	66.995	-5.670	0.00	0.00	6
ATOM	557	C	PRO	72	30.011	65.832	-2.627	0.00	0.00	6
ATOM	558	O	PRO	72	30.783	66.042	-1.695	0.00	0.00	8
ATOM	559	N	PHE	73	28.695	65.802	-2.489	0.00	0.00	7
ATOM	560	CA	PHE	73	28.012	66.098	-1.245	0.00	0.00	6
ATOM	561	CB	PHE	73	27.743	67.609	-1.119	0.00	0.00	6
ATOM	562	CG	PHE	73	27.575	68.324	-2.448	0.00	0.00	6
ATOM	563	CD1	PHE	73	26.419	68.168	-3.212	0.00	0.00	6
ATOM	564	CD2	PHE	73	28.590	69.142	-2.940	0.00	0.00	6
ATOM	565	CE1	PHE	73	26.284	68.814	-4.435	0.00	0.00	6
ATOM	566	CE2	PHE	73	28.453	69.787	-4.167	0.00	0.00	6
ATOM	567	CZ	PHE	73	27.307	69.621	-4.908	0.00	0.00	6
ATOM	568	C	PHE	73	26.721	65.310	-1.303	0.00	0.00	6
ATOM	569	O	PHE	73	26.197	65.073	-2.388	0.00	0.00	8
ATOM	570	N	LEU	74	26.190	64.931	-0.149	0.00	0.00	7
ATOM	571	CA	LEU	74	24.988	64.116	-0.099	0.00	0.00	6
ATOM	572	CB	LEU	74	25.321	62.723	0.458	0.00	0.00	6

FIG.23.8



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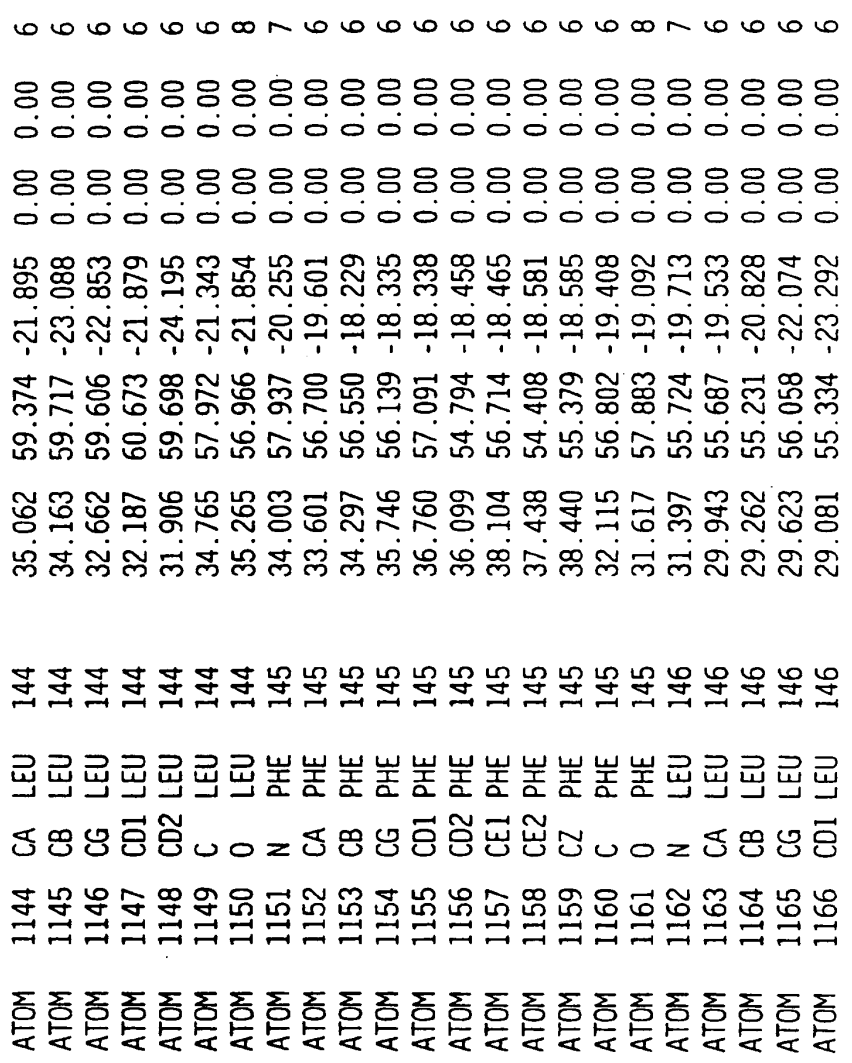
ATOM    573  CG  LEU    74      26.519  61.983  -0.157  0.00  0.00      6
ATOM    574  CD1 LEU    74      26.931  60.816   0.738  0.00  0.00      6
ATOM    575  CD2 LEU    74      26.187  61.499  -1.577  0.00  0.00      6
ATOM    576  C   LEU    74      23.986  64.772   0.769  0.00  0.00      6
ATOM    577  O   LEU    74      24.339  65.469   1.696  0.00  0.00      8
ATOM    578  N   VAL    75      22.724  64.521   0.486  0.00  0.00      7
ATOM    579  CA  VAL    75      21.650  65.118   1.227  0.00  0.00      6
ATOM    580  CB  VAL    75      20.342  65.185   0.360  0.00  0.00      6
ATOM    581  CG1 VAL    75      19.715  63.790   0.159  0.00  0.00      6
ATOM    582  CG2 VAL    75      19.369  66.187   0.936  0.00  0.00      6
ATOM    583  C   VAL    75      21.450  64.417   2.558  0.00  0.00      6
ATOM    584  O   VAL    75      21.570  63.194   2.660  0.00  0.00      8
ATOM    585  N   GLN    76      21.231  65.225   3.587  0.00  0.00      7
ATOM    586  CA  GLN    76      21.027  64.740   4.934  0.00  0.00      6
ATOM    587  CB  GLN    76      21.641  65.720   5.926  0.00  0.00      6
ATOM    588  CG  GLN    76      23.111  65.961   5.650  0.00  0.00      6
ATOM    589  CD  GLN    76      23.908  64.661   5.616  0.00  0.00      6
ATOM    590  OE1 GLN    76      23.813  63.856   6.530  0.00  0.00      8
ATOM    591  NE2 GLN    76      24.673  64.450   4.558  0.00  0.00      7
ATOM    592  C   GLN    76      19.544  64.575   5.137  0.00  0.00      6
ATOM    593  O   GLN    76      18.735  65.178   4.421  0.00  0.00      8
==========================================================================
ATOM   1143  N   LEU   144      36.448  59.438 -22.280  0.00  0.00      7
```

FIG.23.9



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ATOM  1144  CA  LEU  144      35.062  59.374 -21.895  0.00  0.00      6
ATOM  1145  CB  LEU  144      34.163  59.717 -23.088  0.00  0.00      6
ATOM  1146  CG  LEU  144      32.662  59.606 -22.853  0.00  0.00      6
ATOM  1147 CD1  LEU  144      32.187  60.673 -21.879  0.00  0.00      6
ATOM  1148 CD2  LEU  144      31.906  59.698 -24.195  0.00  0.00      6
ATOM  1149  C   LEU  144      34.765  57.972 -21.343  0.00  0.00      6
ATOM  1150  O   LEU  144      35.265  56.966 -21.854  0.00  0.00      8
ATOM  1151  N   PHE  145      34.003  57.937 -20.255  0.00  0.00      7
ATOM  1152  CA  PHE  145      33.601  56.700 -19.601  0.00  0.00      6
ATOM  1153  CB  PHE  145      34.297  56.550 -18.229  0.00  0.00      6
ATOM  1154  CG  PHE  145      35.746  56.139 -18.335  0.00  0.00      6
ATOM  1155 CD1  PHE  145      36.760  57.091 -18.338  0.00  0.00      6
ATOM  1156 CD2  PHE  145      36.099  54.794 -18.458  0.00  0.00      6
ATOM  1157 CE1  PHE  145      38.104  56.714 -18.465  0.00  0.00      6
ATOM  1158 CE2  PHE  145      37.438  54.408 -18.581  0.00  0.00      6
ATOM  1159  CZ  PHE  145      38.440  55.379 -18.585  0.00  0.00      6
ATOM  1160  C   PHE  145      32.115  56.802 -19.408  0.00  0.00      6
ATOM  1161  O   PHE  145      31.617  57.883 -19.092  0.00  0.00      8
ATOM  1162  N   LEU  146      31.397  55.724 -19.713  0.00  0.00      7
ATOM  1163  CA  LEU  146      29.943  55.687 -19.533  0.00  0.00      6
ATOM  1164  CB  LEU  146      29.262  55.231 -20.828  0.00  0.00      6
ATOM  1165  CG  LEU  146      29.623  56.058 -22.074  0.00  0.00      6
ATOM  1166 CD1  LEU  146      29.081  55.334 -23.292  0.00  0.00      6
```

FIG.23.10

```
ATOM   1167  CD2 LEU   146      29.072  57.489 -21.979  0.00  0.00      6
ATOM   1168  C   LEU   146      29.621  54.726 -18.362  0.00  0.00      6
ATOM   1169  O   LEU   146      29.873  53.517 -18.447  0.00  0.00      8
ATOM   1170  N   THR   147      29.055  55.256 -17.278  0.00  0.00      7
ATOM   1171  CA  THR   147      28.776  54.433 -16.105  0.00  0.00      6
ATOM   1172  CB  THR   147      29.745  54.778 -14.961  0.00  0.00      6
ATOM   1173  OG1 THR   147      29.460  56.099 -14.501  0.00  0.00      8
ATOM   1174  CG2 THR   147      31.212  54.724 -15.432  0.00  0.00      6
ATOM   1175  C   THR   147      27.339  54.610 -15.650  0.00  0.00      6
ATOM   1176  O   THR   147      26.719  55.634 -15.900  0.00  0.00      8
ATOM   1177  N   GLY   148      26.788  53.592 -15.001  0.00  0.00      7
ATOM   1178  CA  GLY   148      25.409  53.688 -14.585  0.00  0.00      6
ATOM   1179  C   GLY   148      25.084  52.506 -13.709  0.00  0.00      6
ATOM   1180  O   GLY   148      25.942  51.643 -13.479  0.00  0.00      8
ATOM   1181  N   GLU   149      23.824  52.380 -13.316  0.00  0.00      7
ATOM   1182  CA  GLU   149      23.468  51.306 -12.416  0.00  0.00      6
ATOM   1183  CB  GLU   149      23.665  51.853 -10.986  0.00  0.00      6
ATOM   1184  CG  GLU   149      22.835  51.240  -9.877  0.00  0.00      6
ATOM   1185  CD  GLU   149      22.897  52.051  -8.596  0.00  0.00      6
ATOM   1186  OE1 GLU   149      21.834  52.483  -8.131  0.00  0.00      8
ATOM   1187  OE2 GLU   149      23.999  52.251  -8.057  0.00  0.00      8
ATOM   1188  C   GLU   149      22.043  50.843 -12.622  0.00  0.00      6
ATOM   1189  O   GLU   149      21.222  51.572 -13.185  0.00  0.00      8
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FIG.23.11

ATOM	1190	N	SER	150	21.767	49.592	-12.278	0.00	0.00	7
ATOM	1191	CA	SER	150	20.400	49.105	-12.366	0.00	0.00	6
ATOM	1192	CB	SER	150	19.522	50.063	-11.538	0.00	0.00	6
ATOM	1193	OG	SER	150	18.222	49.539	-11.251	0.00	0.00	8
ATOM	1194	C	SER	150	19.904	48.980	-13.825	0.00	0.00	6
ATOM	1195	O	SER	150	20.505	48.270	-14.622	0.00	0.00	8
ATOM	1196	N	TYR	151	18.822	49.675	-14.177	0.00	0.00	7
ATOM	1197	CA	TYR	151	18.302	49.623	-15.533	0.00	0.00	6
ATOM	1198	CB	TYR	151	16.965	50.337	-15.675	0.00	0.00	6
ATOM	1199	CG	TYR	151	16.241	49.935	-16.945	0.00	0.00	6
ATOM	1200	CD1	TYR	151	15.527	48.751	-16.995	0.00	0.00	6
ATOM	1201	CE1	TYR	151	14.953	48.306	-18.157	0.00	0.00	6
ATOM	1202	CD2	TYR	151	16.356	50.679	-18.115	0.00	0.00	6
ATOM	1203	CE2	TYR	151	15.788	50.242	-19.290	0.00	0.00	6
ATOM	1204	CZ	TYR	151	15.089	49.047	-19.298	0.00	0.00	6
ATOM	1205	OH	TYR	151	14.497	48.570	-20.435	0.00	0.00	8
ATOM	1206	C	TYR	151	19.315	50.228	-16.485	0.00	0.00	6
ATOM	1207	O	TYR	151	19.260	49.965	-17.683	0.00	0.00	8
ATOM	1208	N	ALA	152	20.259	51.018	-15.965	0.00	0.00	7
ATOM	1209	CA	ALA	152	21.288	51.581	-16.813	0.00	0.00	6
ATOM	1210	CB	ALA	152	22.089	52.610	-16.082	0.00	0.00	6
ATOM	1211	C	ALA	152	22.186	50.433	-17.271	0.00	0.00	6
ATOM	1212	O	ALA	152	23.256	50.657	-17.804	0.00	0.00	8

FIG.23.12

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ATOM   1213  N   GLY   153      21.796  49.198  -16.961  0.00  0.00      7
ATOM   1214  CA  GLY   153      22.536  48.043  -17.429  0.00  0.00      6
ATOM   1215  C   GLY   153      22.133  47.843  -18.889  0.00  0.00      6
ATOM   1216  O   GLY   153      22.790  47.120  -19.639  0.00  0.00      8
ATOM   1217  N   ILE   154      20.980  48.407  -19.249  0.00  0.00      7
ATOM   1218  CA  ILE   154      20.462  48.384  -20.627  0.00  0.00      6
ATOM   1219  CB  ILE   154      18.911  48.220  -20.665  0.00  0.00      6
ATOM   1220  CG2 ILE   154      18.394  48.228  -22.129  0.00  0.00      6
ATOM   1221  CG1 ILE   154      18.441  46.989  -19.861  0.00  0.00      6
ATOM   1222  CD1 ILE   154      18.441  45.716  -20.587  0.00  0.00      6
ATOM   1223  C   ILE   154      20.845  49.759  -21.247  0.00  0.00      6
ATOM   1224  O   ILE   154      21.425  49.819  -22.324  0.00  0.00      8
ATOM   1225  N   TYR   155      20.578  50.854  -20.535  0.00  0.00      7
ATOM   1226  CA  TYR   155      20.918  52.193  -21.022  0.00  0.00      6
ATOM   1227  CB  TYR   155      20.694  53.278  -19.950  0.00  0.00      6
ATOM   1228  CG  TYR   155      19.300  53.539  -19.449  0.00  0.00      6
ATOM   1229  CD1 TYR   155      19.117  54.164  -18.226  0.00  0.00      6
ATOM   1230  CE1 TYR   155      17.846  54.508  -17.779  0.00  0.00      6
ATOM   1231  CD2 TYR   155      18.179  53.252  -20.210  0.00  0.00      6
ATOM   1232  CE2 TYR   155      16.912  53.579  -19.775  0.00  0.00      6
ATOM   1233  CZ  TYR   155      16.752  54.215  -18.558  0.00  0.00      6
ATOM   1234  OH  TYR   155      15.510  54.595  -18.114  0.00  0.00      8
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FIG.23.13

ATOM	1235	C	TYR	155	22.378	52.340	-21.436	0.00	0.00	6
ATOM	1236	O	TYR	155	22.691	52.886	-22.497	0.00	0.00	8
ATOM	1365	N	GLY	173	35.881	53.475	-21.853	0.00	0.00	7
ATOM	1366	CA	GLY	173	35.360	52.368	-21.082	0.00	0.00	6
ATOM	1367	C	GLY	173	33.978	52.596	-20.551	0.00	0.00	6
ATOM	1368	O	GLY	173	33.420	53.674	-20.690	0.00	0.00	8
ATOM	1369	N	LEU	174	33.401	51.545	-19.983	0.00	0.00	7
ATOM	1370	CA	LEU	174	32.074	51.619	-19.384	0.00	0.00	6
ATOM	1371	CB	LEU	174	30.977	51.192	-20.377	0.00	0.00	6
ATOM	1372	CG	LEU	174	31.094	49.922	-21.229	0.00	0.00	6
ATOM	1373	CD1	LEU	174	29.715	49.504	-21.640	0.00	0.00	6
ATOM	1374	CD2	LEU	174	31.989	50.148	-22.413	0.00	0.00	6
ATOM	1375	C	LEU	174	32.045	50.765	-18.112	0.00	0.00	6
ATOM	1376	O	LEU	174	32.846	49.837	-17.967	0.00	0.00	8
ATOM	1377	N	ALA	175	31.182	51.131	-17.172	0.00	0.00	7
ATOM	1378	CA	ALA	175	31.060	50.408	-15.914	0.00	0.00	6
ATOM	1379	CB	ALA	175	31.896	51.072	-14.833	0.00	0.00	6
ATOM	1380	C	ALA	175	29.615	50.378	-15.510	0.00	0.00	6
ATOM	1381	O	ALA	175	28.936	51.408	-15.528	0.00	0.00	8
ATOM	1382	N	VAL	176	29.130	49.187	-15.171	0.00	0.00	7
ATOM	1383	CA	VAL	176	27.736	49.007	-14.783	0.00	0.00	6
ATOM	1384	CB	VAL	176	26.985	48.172	-15.858	0.00	0.00	6

FIG.23.14

ATOM	1385	CG1	VAL	176	25.619	47.729	-15.337	0.00	0.00	6
ATOM	1386	CG2	VAL	176	26.802	49.018	-17.145	0.00	0.00	6
ATOM	1387	C	VAL	176	27.608	48.356	-13.402	0.00	0.00	6
ATOM	1388	O	VAL	176	28.162	47.268	-13.157	0.00	0.00	8
ATOM	1389	N	GLY	177	26.816	48.980	-12.533	0.00	0.00	7
ATOM	1390	CA	GLY	177	26.652	48.476	-11.187	0.00	0.00	6
ATOM	1391	C	GLY	177	25.308	47.860	-11.030	0.00	0.00	6
ATOM	1392	O	GLY	177	24.314	48.505	-11.369	0.00	0.00	8
ATOM	1393	N	ASN	178	25.263	46.625	-10.524	0.00	0.00	7
ATOM	1394	CA	ASN	178	23.996	45.890	-10.352	0.00	0.00	6
ATOM	1395	CB	ASN	178	23.302	46.250	-9.038	0.00	0.00	6
ATOM	1396	CG	ASN	178	24.002	45.646	-7.845	0.00	0.00	6
ATOM	1397	OD1	ASN	178	25.088	46.082	-7.486	0.00	0.00	8
ATOM	1398	ND2	ASN	178	23.470	44.542	-7.328	0.00	0.00	7
ATOM	1399	C	ASN	178	23.079	46.132	-11.520	0.00	0.00	6
ATOM	1400	O	ASN	178	21.897	46.472	-11.358	0.00	0.00	8
ATOM	1401	N	GLY	179	23.639	45.931	-12.708	0.00	0.00	7
ATOM	1402	CA	GLY	179	22.891	46.171	-13.923	0.00	0.00	6
ATOM	1403	C	GLY	179	22.028	45.045	-14.409	0.00	0.00	6
ATOM	1404	O	GLY	179	22.367	43.883	-14.231	0.00	0.00	8
ATOM	1405	N	LEU	180	20.913	45.399	-15.033	0.00	0.00	7
ATOM	1406	CA	LEU	180	19.988	44.434	-15.597	0.00	0.00	6
ATOM	1407	CB	LEU	180	18.578	45.029	-15.601	0.00	0.00	6

FIG.23.15

ATOM	1408	CG	LEU	180	17.450	44.240	-16.246	0.00	0.00	6
ATOM	1409	CD1	LEU	180	17.328	42.882	-15.581	0.00	0.00	6
ATOM	1410	CD2	LEU	180	16.156	45.021	-16.128	0.00	0.00	6
ATOM	1411	C	LEU	180	20.450	44.069	-17.025	0.00	0.00	6
ATOM	1412	O	LEU	180	19.909	44.564	-18.017	0.00	0.00	8
ATOM	1413	N	SER	181	21.471	43.214	-17.106	0.00	0.00	7
ATOM	1414	CA	SER	181	22.058	42.756	-18.365	0.00	0.00	6
ATOM	1415	CB	SER	181	23.453	42.206	-18.127	0.00	0.00	6
ATOM	1416	OG	SER	181	24.275	43.134	-17.462	0.00	0.00	8
ATOM	1417	C	SER	181	21.271	41.650	-19.020	0.00	0.00	6
ATOM	1418	O	SER	181	21.415	41.422	-20.215	0.00	0.00	8
ATOM	1419	N	SER	182	20.469	40.934	-18.242	0.00	0.00	7
ATOM	1420	CA	SER	182	19.716	39.839	-18.799	0.00	0.00	6
ATOM	1421	CB	SER	182	20.641	38.637	-18.997	0.00	0.00	6
ATOM	1422	OG	SER	182	19.892	37.518	-19.423	0.00	0.00	8
ATOM	1423	C	SER	182	18.557	39.448	-17.921	0.00	0.00	6
ATOM	1424	O	SER	182	18.745	38.985	-16.806	0.00	0.00	8
ATOM	1425	N	TYR	183	17.354	39.590	-18.450	0.00	0.00	7
ATOM	1426	CA	TYR	183	16.165	39.240	-17.702	0.00	0.00	6
ATOM	1427	CB	TYR	183	14.922	39.574	-18.504	0.00	0.00	6
ATOM	1428	CG	TYR	183	14.706	41.046	-18.733	0.00	0.00	6
ATOM	1429	CD1	TYR	183	15.358	41.720	-19.769	0.00	0.00	6
ATOM	1430	CE1	TYR	183	15.136	43.095	-19.998	0.00	0.00	6

FIG.23.16

ATOM	1431	CD2	TYR	183	13.827	41.776	-17.930	0.00	0.00	6
ATOM	1432	CE2	TYR	183	13.594	43.152	-18.162	0.00	0.00	6
ATOM	1433	CZ	TYR	183	14.248	43.800	-19.195	0.00	0.00	6
ATOM	1434	OH	TYR	183	13.965	45.123	-19.446	0.00	0.00	8
ATOM	1435	C	TYR	183	16.152	37.765	-17.303	0.00	0.00	6
ATOM	1436	O	TYR	183	15.857	37.435	-16.157	0.00	0.00	8
ATOM	1437	N	GLU	184	16.503	36.888	-18.235	0.00	0.00	7
ATOM	1438	CA	GLU	184	16.518	35.453	-17.969	0.00	0.00	6
ATOM	1439	CB	GLU	184	16.814	34.658	-19.241	0.00	0.00	6
ATOM	1440	CG	GLU	184	16.886	33.140	-18.995	0.00	0.00	6
ATOM	1441	CD	GLU	184	16.499	32.303	-20.211	0.00	0.00	6
ATOM	1442	OE1	GLU	184	16.775	32.730	-21.350	0.00	0.00	8
ATOM	1443	OE2	GLU	184	15.923	31.207	-20.012	0.00	0.00	8
ATOM	1444	C	GLU	184	17.527	35.079	-16.909	0.00	0.00	6
ATOM	1445	O	GLU	184	17.227	34.308	-15.992	0.00	0.00	8
ATOM	1446	N	GLN	185	18.745	35.575	-17.061	0.00	0.00	7
ATOM	1447	CA	GLN	185	19.772	35.280	-16.089	0.00	0.00	6
ATOM	1448	CB	GLN	185	21.141	35.599	-16.634	0.00	0.00	6
ATOM	1449	CG	GLN	185	21.648	34.401	-17.374	0.00	0.00	6
ATOM	1450	CD	GLN	185	22.880	34.683	-18.133	0.00	0.00	6
ATOM	1451	OE1	GLN	185	23.157	35.818	-18.479	0.00	0.00	8
ATOM	1452	NE2	GLN	185	23.650	33.649	-18.401	0.00	0.00	7
ATOM	1453	C	GLN	185	19.534	35.908	-14.740	0.00	0.00	6

FIG.23.17

ATOM	1454	O	GLN	185	19.933	35.364	-13.723	0.00	0.00	8
ATOM	1455	N	ASN	186	18.803	37.006	-14.723	0.00	0.00	7
ATOM	1456	CA	ASN	186	18.492	37.660	-13.474	0.00	0.00	6
ATOM	1457	CB	ASN	186	17.961	39.071	-13.717	0.00	0.00	6
ATOM	1458	CG	ASN	186	17.954	39.896	-12.461	0.00	0.00	6
ATOM	1459	OD1	ASN	186	18.911	39.849	-11.687	0.00	0.00	8
ATOM	1460	ND2	ASN	186	16.904	40.668	-12.258	0.00	0.00	7
ATOM	1461	C	ASN	186	17.448	36.848	-12.721	0.00	0.00	6
ATOM	1462	O	ASN	186	17.591	36.612	-11.537	0.00	0.00	8
ATOM	1463	N	ASP	187	16.385	36.449	-13.413	0.00	0.00	7
ATOM	1464	CA	ASP	187	15.306	35.669	-12.829	0.00	0.00	6
ATOM	1465	CB	ASP	187	14.163	35.536	-13.837	0.00	0.00	6
ATOM	1466	CG	ASP	187	13.300	36.786	-13.931	0.00	0.00	6
ATOM	1467	OD1	ASP	187	13.622	37.809	-13.275	0.00	0.00	8
ATOM	1468	OD2	ASP	187	12.277	36.740	-14.656	0.00	0.00	8
ATOM	1469	C	ASP	187	15.697	34.272	-12.321	0.00	0.00	6
ATOM	1470	O	ASP	187	15.216	33.837	-11.275	0.00	0.00	8
ATOM	1471	N	ASN	188	16.506	33.546	-13.089	0.00	0.00	7
ATOM	1472	CA	ASN	188	16.924	32.187	-12.713	0.00	0.00	6
ATOM	1473	CB	ASN	188	17.620	31.448	-13.881	0.00	0.00	6
ATOM	1474	CG	ASN	188	16.659	31.067	-15.021	0.00	0.00	6
ATOM	1475	OD1	ASN	188	15.504	30.705	-14.798	0.00	0.00	8
ATOM	1476	ND2	ASN	188	17.147	31.172	-16.260	0.00	0.00	7

FIG.23.18

ATOM	1477	C	ASN	188	17.874	32.200	-11.521	0.00	0.00	6
ATOM	1478	O	ASN	188	17.812	31.330	-10.660	0.00	0.00	8
ATOM	1479	N	SER	189	18.813	33.133	-11.513	0.00	0.00	7
ATOM	1480	CA	SER	189	19.763	33.204	-10.418	0.00	0.00	6
ATOM	1481	CB	SER	189	20.983	34.036	-10.823	0.00	0.00	6
ATOM	1482	OG	SER	189	20.613	35.349	-11.194	0.00	0.00	8
ATOM	1483	C	SER	189	19.109	33.752	-9.136	0.00	0.00	6
ATOM	1484	O	SER	189	19.513	33.410	-8.029	0.00	0.00	8
ATOM	1485	N	LEU	190	18.059	34.539	-9.287	0.00	0.00	7
ATOM	1486	CA	LEU	190	17.359	35.123	-8.145	0.00	0.00	6
ATOM	1487	CB	LEU	190	16.368	36.189	-8.628	0.00	0.00	6
ATOM	1488	CG	LEU	190	15.576	36.873	-7.522	0.00	0.00	6
ATOM	1489	CD1	LEU	190	16.557	37.491	-6.538	0.00	0.00	6
ATOM	1490	CD2	LEU	190	14.621	37.921	-8.103	0.00	0.00	6
ATOM	1491	C	LEU	190	16.622	34.060	-7.305	0.00	0.00	6
ATOM	1492	O	LEU	190	16.500	34.187	-6.089	0.00	0.00	8
ATOM	1493	N	VAL	191	16.099	33.029	-7.960	0.00	0.00	7
ATOM	1494	CA	VAL	191	15.397	31.964	-7.264	0.00	0.00	6
ATOM	1495	CB	VAL	191	14.585	31.109	-8.260	0.00	0.00	6
ATOM	1496	CG1	VAL	191	13.787	30.007	-7.541	0.00	0.00	6
ATOM	1497	CG2	VAL	191	13.586	32.016	-8.970	0.00	0.00	6
ATOM	1498	C	VAL	191	16.426	31.177	-6.465	0.00	0.00	6
ATOM	1499	O	VAL	191	16.215	30.897	-5.305	0.00	0.00	8

FIG.23.19

ATOM	1500	N	TYR	192	17.568	30.883	-7.061	0.00	0.00	7
ATOM	1501	CA	TYR	192	18.619	30.192	-6.341	0.00	0.00	6
ATOM	1502	CB	TYR	192	19.861	30.017	-7.232	0.00	0.00	6
ATOM	1503	CG	TYR	192	19.740	28.862	-8.188	0.00	0.00	6
ATOM	1504	CD1	TYR	192	19.292	29.057	-9.486	0.00	0.00	6
ATOM	1505	CE1	TYR	192	19.083	27.987	-10.339	0.00	0.00	6
ATOM	1506	CD2	TYR	192	19.988	27.555	-7.766	0.00	0.00	6
ATOM	1507	CE2	TYR	192	19.780	26.479	-8.608	0.00	0.00	6
ATOM	1508	CZ	TYR	192	19.324	26.703	-9.897	0.00	0.00	6
ATOM	1509	OH	TYR	192	19.110	25.652	-10.741	0.00	0.00	8
ATOM	1510	C	TYR	192	18.996	31.068	-5.159	0.00	0.00	6
ATOM	1511	O	TYR	192	19.161	30.577	-4.040	0.00	0.00	8
ATOM	1512	N	PHE	193	19.178	32.359	-5.445	0.00	0.00	7
ATOM	1513	CA	PHE	193	19.562	33.354	-4.461	0.00	0.00	6
ATOM	1514	CB	PHE	193	19.555	34.762	-5.087	0.00	0.00	6
ATOM	1515	CG	PHE	193	20.179	35.836	-4.213	0.00	0.00	6
ATOM	1516	CD1	PHE	193	21.454	36.306	-4.480	0.00	0.00	6
ATOM	1517	CD2	PHE	193	19.473	36.385	-3.130	0.00	0.00	6
ATOM	1518	CE1	PHE	193	22.035	37.308	-3.696	0.00	0.00	6
ATOM	1519	CE2	PHE	193	20.043	37.395	-2.331	0.00	0.00	6
ATOM	1520	CZ	PHE	193	21.325	37.854	-2.618	0.00	0.00	6
ATOM	1521	C	PHE	193	18.589	33.280	-3.315	0.00	0.00	6
ATOM	1522	O	PHE	193	18.991	33.125	-2.175	0.00	0.00	8

FIG.23.20

ATOM	1523	N	ALA	194	17.309	33.328	-3.631	0.00	0.00	7
ATOM	1524	CA	ALA	194	16.274	33.290	-2.619	0.00	0.00	6
ATOM	1525	CB	ALA	194	14.902	33.295	-3.278	0.00	0.00	6
ATOM	1526	C	ALA	194	16.430	32.089	-1.677	0.00	0.00	6
ATOM	1527	O	ALA	194	16.449	32.244	-0.451	0.00	0.00	8
ATOM	1528	N	TYR	195	16.633	30.906	-2.237	0.00	0.00	7
ATOM	1529	CA	TYR	195	16.770	29.709	-1.416	0.00	0.00	6
ATOM	1530	CB	TYR	195	16.754	28.455	-2.297	0.00	0.00	6
ATOM	1531	CG	TYR	195	16.807	27.147	-1.518	0.00	0.00	6
ATOM	1532	CD1	TYR	195	15.793	26.795	-0.622	0.00	0.00	6
ATOM	1533	CE1	TYR	195	15.881	25.625	0.136	0.00	0.00	6
ATOM	1534	CD2	TYR	195	17.899	26.283	-1.645	0.00	0.00	6
ATOM	1535	CE2	TYR	195	17.986	25.099	-0.895	0.00	0.00	6
ATOM	1536	CZ	TYR	195	16.983	24.787	-0.006	0.00	0.00	6
ATOM	1537	OH	TYR	195	17.120	23.664	0.771	0.00	0.00	8
ATOM	1538	C	TYR	195	18.019	29.712	-0.541	0.00	0.00	6
ATOM	1539	O	TYR	195	17.948	29.581	0.685	0.00	0.00	8
ATOM	1540	N	TYR	196	19.165	29.887	-1.178	0.00	0.00	7
ATOM	1541	CA	TYR	196	20.421	29.865	-0.475	0.00	0.00	6
ATOM	1542	CB	TYR	196	21.585	29.653	-1.453	0.00	0.00	6
ATOM	1543	CG	TYR	196	21.526	28.262	-2.071	0.00	0.00	6
ATOM	1544	CD1	TYR	196	20.932	28.057	-3.327	0.00	0.00	6
ATOM	1545	CE1	TYR	196	20.744	26.773	-3.846	0.00	0.00	6

FIG.23.21

ATOM	1546	CD2	TYR	196	21.951	27.121	-1.355	0.00	0.00	6
ATOM	1547	CE2	TYR	196	21.769	25.826	-1.878	0.00	0.00	6
ATOM	1548	CZ	TYR	196	21.155	25.674	-3.117	0.00	0.00	6
ATOM	1549	OH	TYR	196	20.864	24.438	-3.599	0.00	0.00	8
ATOM	1550	C	TYR	196	20.640	31.013	0.479	0.00	0.00	6
ATOM	1551	O	TYR	196	21.617	31.000	1.222	0.00	0.00	8
ATOM	1552	N	HIS	197	19.760	32.020	0.434	0.00	0.00	7
ATOM	1553	CA	HIS	197	19.845	33.145	1.366	0.00	0.00	6
ATOM	1554	CB	HIS	197	19.837	34.508	0.655	0.00	0.00	6
ATOM	1555	CG	HIS	197	21.117	34.805	-0.067	0.00	0.00	6
ATOM	1556	CD2	HIS	197	21.637	34.292	-1.208	0.00	0.00	6
ATOM	1557	ND1	HIS	197	22.062	35.673	0.425	0.00	0.00	7
ATOM	1558	CE1	HIS	197	23.116	35.679	-0.375	0.00	0.00	6
ATOM	1559	NE2	HIS	197	22.884	34.848	-1.373	0.00	0.00	7
ATOM	1560	C	HIS	197	18.781	33.008	2.455	0.00	0.00	6
ATOM	1561	O	HIS	197	18.656	33.855	3.338	0.00	0.00	8
ATOM	1779	N	LEU	226	2.352	24.910	-15.190	0.00	0.00	7
ATOM	1780	CA	LEU	226	1.463	25.680	-14.329	0.00	0.00	6
ATOM	1781	CB	LEU	226	0.022	25.288	-14.600	0.00	0.00	6
ATOM	1782	CG	LEU	226	-0.385	25.876	-15.950	0.00	0.00	6
ATOM	1783	CD1	LEU	226	-1.496	25.041	-16.590	0.00	0.00	6
ATOM	1784	CD2	LEU	226	-0.802	27.332	-15.735	0.00	0.00	6

FIG.23.22

```
ATOM   1785  C   LEU  226      1.743  25.695 -12.833  0.00  0.00      6
ATOM   1786  O   LEU  226      1.491  26.698 -12.166  0.00  0.00      8
ATOM   1787  N   GLU  227      2.227  24.583 -12.296  0.00  0.00      7
ATOM   1788  CA  GLU  227      2.548  24.524 -10.874  0.00  0.00      6
ATOM   1789  CB  GLU  227      2.532  23.086 -10.383  0.00  0.00      6
ATOM   1790  CG  GLU  227      1.139  22.494 -10.521  0.00  0.00      6
ATOM   1791  CD  GLU  227      1.019  21.103  -9.943  0.00  0.00      6
ATOM   1792  OE1 GLU  227      0.888  20.998  -8.699  0.00  0.00      8
ATOM   1793  OE2 GLU  227      1.048  20.124 -10.734  0.00  0.00      8
ATOM   1794  C   GLU  227      3.889  25.207 -10.631  0.00  0.00      6
ATOM   1795  O   GLU  227      4.097  25.850  -9.602  0.00  0.00      8
ATOM   1796  N   CYS  228      4.775  25.097 -11.611  0.00  0.00      7
ATOM   1797  CA  CYS  228      6.062  25.758 -11.560  0.00  0.00      6
ATOM   1798  C   CYS  228      5.799  27.269 -11.508  0.00  0.00      6
ATOM   1799  O   CYS  228      6.400  27.994 -10.734  0.00  0.00      8
ATOM   1800  CB  CYS  228      6.840  25.463 -12.812  0.00  0.00      6
ATOM   1801  SG  CYS  228      8.238  26.583 -12.943  0.00  0.00     16
ATOM   1802  N   VAL  229      4.870  27.729 -12.331  0.00  0.00      7
ATOM   1803  CA  VAL  229      4.492  29.131 -12.370  0.00  0.00      6
ATOM   1804  CB  VAL  229      3.510  29.402 -13.531  0.00  0.00      6
ATOM   1805  CG1 VAL  229      2.830  30.758 -13.367  0.00  0.00      6
ATOM   1806  CG2 VAL  229      4.248  29.311 -14.858  0.00  0.00      6
ATOM   1807  C   VAL  229      3.869  29.539 -11.039  0.00  0.00      6
```

FIG.23.23

ATOM	1808	O	VAL	229	4.072	30.652	-10.577	0.00	0.00	8
ATOM	1809	N	THR	230	3.085	28.656	-10.436	0.00	0.00	7
ATOM	1810	CA	THR	230	2.461	28.950	-9.142	0.00	0.00	6
ATOM	1811	CB	THR	230	1.448	27.841	-8.748	0.00	0.00	6
ATOM	1812	OG1	THR	230	0.497	27.680	-9.808	0.00	0.00	8
ATOM	1813	CG2	THR	230	0.688	28.211	-7.486	0.00	0.00	6
ATOM	1814	C	THR	230	3.555	29.111	-8.069	0.00	0.00	6
ATOM	1815	O	THR	230	3.474	29.988	-7.197	0.00	0.00	8
ATOM	1816	N	ASN	231	4.600	28.295	-8.172	0.00	0.00	7
ATOM	1817	CA	ASN	231	5.719	28.372	-7.253	0.00	0.00	6
ATOM	1818	CB	ASN	231	6.628	27.166	-7.428	0.00	0.00	6
ATOM	1819	CG	ASN	231	5.975	25.877	-6.984	0.00	0.00	6
ATOM	1820	OD1	ASN	231	6.433	24.799	-7.349	0.00	0.00	8
ATOM	1821	ND2	ASN	231	4.912	25.972	-6.187	0.00	0.00	7
ATOM	1822	C	ASN	231	6.511	29.661	-7.493	0.00	0.00	6
ATOM	1823	O	ASN	231	6.833	30.370	-6.543	0.00	0.00	8
ATOM	1824	N	LEU	232	6.838	29.946	-8.757	0.00	0.00	7
ATOM	1825	CA	LEU	232	7.572	31.165	-9.123	0.00	0.00	6
ATOM	1826	CB	LEU	232	7.903	31.194	-10.608	0.00	0.00	6
ATOM	1827	CG	LEU	232	8.945	30.168	-11.006	0.00	0.00	6
ATOM	1828	CD1	LEU	232	9.161	30.243	-12.517	0.00	0.00	6
ATOM	1829	CD2	LEU	232	10.235	30.440	-10.257	0.00	0.00	6
ATOM	1830	C	LEU	232	6.821	32.435	-8.719	0.00	0.00	6

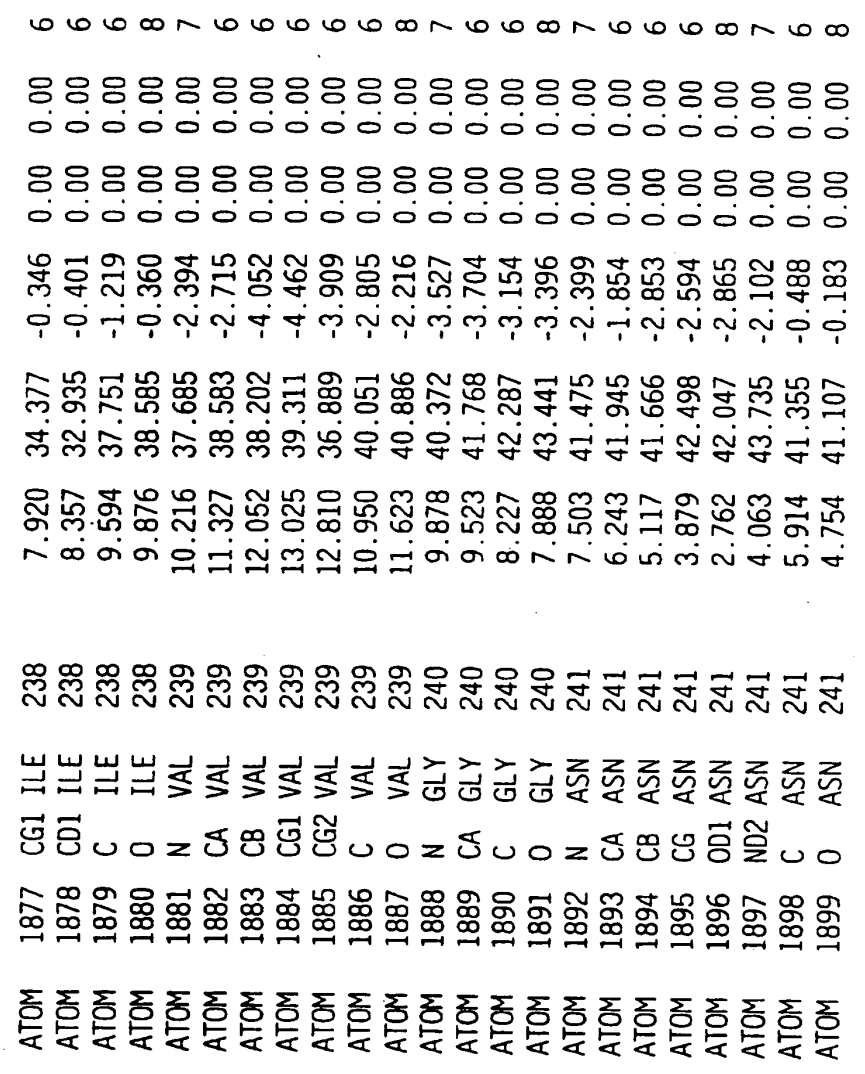
FIG:23.24

```
ATOM  1831  O   LEU 232      7.439  33.410  -8.328  0.00  0.00      8
ATOM  1832  N   GLN 233      5.502  32.429  -8.785  0.00  0.00      7
ATOM  1833  CA  GLN 233      4.748  33.601  -8.364  0.00  0.00      6
ATOM  1834  CB  GLN 233      3.275  33.477  -8.749  0.00  0.00      6
ATOM  1835  CG  GLN 233      2.983  33.724 -10.239  0.00  0.00      6
ATOM  1836  CD  GLN 233      1.541  33.424 -10.596  0.00  0.00      6
ATOM  1837  OE1 GLN 233      0.909  34.149 -11.371  0.00  0.00      8
ATOM  1838  NE2 GLN 233      1.008  32.348 -10.028  0.00  0.00      7
ATOM  1839  C   GLN 233      4.901  33.816  -6.850  0.00  0.00      6
ATOM  1840  O   GLN 233      4.820  34.961  -6.365  0.00  0.00      8
ATOM  1841  N   GLU 234      5.120  32.722  -6.113  0.00  0.00      7
ATOM  1842  CA  GLU 234      5.311  32.767  -4.660  0.00  0.00      6
ATOM  1843  CB  GLU 234      5.132  31.382  -4.040  0.00  0.00      6
ATOM  1844  CG  GLU 234      5.527  31.310  -2.556  0.00  0.00      6
ATOM  1845  CD  GLU 234      4.629  32.135  -1.615  0.00  0.00      6
ATOM  1846  OE1 GLU 234      3.659  32.805  -2.049  0.00  0.00      8
ATOM  1847  OE2 GLU 234      4.896  32.100  -0.396  0.00  0.00      8
ATOM  1848  C   GLU 234      6.704  33.267  -4.335  0.00  0.00      6
ATOM  1849  O   GLU 234      6.923  33.956  -3.342  0.00  0.00      8
ATOM  1850  N   VAL 235      7.665  32.832  -5.126  0.00  0.00      7
ATOM  1851  CA  VAL 235      9.018  33.293  -4.952  0.00  0.00      6
ATOM  1852  CB  VAL 235      9.927  32.575  -5.925  0.00  0.00      6
ATOM  1853  CG1 VAL 235     11.347  33.107  -5.808  0.00  0.00      6
```

FIG.23.25

ATOM	1854	CG2	VAL	235	9.862	31.077	-5.668	0.00	0.00	6
ATOM	1855	C	VAL	235	9.076	34.827	-5.208	0.00	0.00	6
ATOM	1856	O	VAL	235	9.716	35.580	-4.464	0.00	0.00	8
ATOM	1857	N	ALA	236	8.372	35.286	-6.241	0.00	0.00	7
ATOM	1858	CA	ALA	236	8.332	36.712	-6.600	0.00	0.00	6
ATOM	1859	CB	ALA	236	7.527	36.908	-7.877	0.00	0.00	6
ATOM	1860	C	ALA	236	7.718	37.538	-5.472	0.00	0.00	6
ATOM	1861	O	ALA	236	8.168	38.650	-5.202	0.00	0.00	8
ATOM	1862	N	ARG	237	6.680	36.997	-4.830	0.00	0.00	7
ATOM	1863	CA	ARG	237	5.996	37.660	-3.714	0.00	0.00	6
ATOM	1864	CB	ARG	237	4.754	36.878	-3.301	0.00	0.00	6
ATOM	1865	CG	ARG	237	4.043	37.521	-2.130	0.00	0.00	6
ATOM	1866	CD	ARG	237	3.006	36.601	-1.550	0.00	0.00	6
ATOM	1867	NE	ARG	237	3.614	35.536	-0.759	0.00	0.00	7
ATOM	1868	CZ	ARG	237	4.155	35.721	0.437	0.00	0.00	6
ATOM	1869	NH1	ARG	237	4.164	36.928	0.977	0.00	0.00	7
ATOM	1870	NH2	ARG	237	4.692	34.700	1.083	0.00	0.00	7
ATOM	1871	C	ARG	237	6.890	37.801	-2.488	0.00	0.00	6
ATOM	1872	O	ARG	237	6.926	38.845	-1.841	0.00	0.00	8
ATOM	1873	N	ILE	238	7.593	36.733	-2.147	0.00	0.00	7
ATOM	1874	CA	ILE	238	8.464	36.760	-0.985	0.00	0.00	6
ATOM	1875	CB	ILE	238	9.048	35.358	-0.686	0.00	0.00	6
ATOM	1876	CG2	ILE	238	10.144	35.452	0.384	0.00	0.00	6

FIG.23.26



ATOM	1877	CG1	ILE	238	7.920	34.377	-0.346	0.00	0.00	6
ATOM	1878	CD1	ILE	238	8.357	32.935	-0.401	0.00	0.00	6
ATOM	1879	C	ILE	238	9.594	37.751	-1.219	0.00	0.00	6
ATOM	1880	O	ILE	238	9.876	38.585	-0.360	0.00	0.00	8
ATOM	1881	N	VAL	239	10.216	37.685	-2.394	0.00	0.00	7
ATOM	1882	CA	VAL	239	11.327	38.583	-2.715	0.00	0.00	6
ATOM	1883	CB	VAL	239	12.052	38.202	-4.052	0.00	0.00	6
ATOM	1884	CG1	VAL	239	13.025	39.311	-4.462	0.00	0.00	6
ATOM	1885	CG2	VAL	239	12.810	36.889	-3.909	0.00	0.00	6
ATOM	1886	C	VAL	239	10.950	40.051	-2.805	0.00	0.00	6
ATOM	1887	O	VAL	239	11.623	40.886	-2.216	0.00	0.00	8
ATOM	1888	N	GLY	240	9.878	40.372	-3.527	0.00	0.00	7
ATOM	1889	CA	GLY	240	9.523	41.768	-3.704	0.00	0.00	6
ATOM	1890	C	GLY	240	8.227	42.287	-3.154	0.00	0.00	6
ATOM	1891	O	GLY	240	7.888	43.441	-3.396	0.00	0.00	8
ATOM	1892	N	ASN	241	7.503	41.475	-2.399	0.00	0.00	7
ATOM	1893	CA	ASN	241	6.243	41.945	-1.854	0.00	0.00	6
ATOM	1894	CB	ASN	241	5.117	41.666	-2.853	0.00	0.00	6
ATOM	1895	CG	ASN	241	3.879	42.498	-2.594	0.00	0.00	6
ATOM	1896	OD1	ASN	241	2.762	42.047	-2.865	0.00	0.00	8
ATOM	1897	ND2	ASN	241	4.063	43.735	-2.102	0.00	0.00	7
ATOM	1898	C	ASN	241	5.914	41.355	-0.488	0.00	0.00	6
ATOM	1899	O	ASN	241	4.754	41.107	-0.183	0.00	0.00	8

FIG.23.27

```
ATOM   1900  N   SER  242      6.931  41.168   0.348  0.00  0.00      7
ATOM   1901  CA  SER  242      6.706  40.614   1.686  0.00  0.00      6
ATOM   1902  CB  SER  242      7.240  39.176   1.763  0.00  0.00      6
ATOM   1903  OG  SER  242      8.648  39.160   1.867  0.00  0.00      8
ATOM   1904  C   SER  242      7.258  41.448   2.864  0.00  0.00      6
ATOM   1905  O   SER  242      7.038  41.096   4.023  0.00  0.00      8
ATOM   1906  N   GLY  243      7.943  42.552   2.568  0.00  0.00      7
ATOM   1907  CA  GLY  243      8.512  43.380   3.610  0.00  0.00      6
ATOM   1908  C   GLY  243     10.021  43.394   3.574  0.00  0.00      6
ATOM   1909  O   GLY  243     10.667  44.122   4.307  0.00  0.00      8
ATOM   1910  N   LEU  244     10.604  42.545   2.749  0.00  0.00      7
ATOM   1911  CA  LEU  244     12.050  42.502   2.620  0.00  0.00      6
ATOM   1912  CB  LEU  244     12.537  41.145   2.067  0.00  0.00      6
ATOM   1913  CG  LEU  244     12.208  39.814   2.778  0.00  0.00      6
ATOM   1914  CD1 LEU  244     12.508  38.640   1.852  0.00  0.00      6
ATOM   1915  CD2 LEU  244     13.009  39.696   4.071  0.00  0.00      6
ATOM   1916  C   LEU  244     12.399  43.598   1.617  0.00  0.00      6
ATOM   1917  O   LEU  244     11.609  43.936   0.713  0.00  0.00      8
ATOM   1918  N   ASN  245     13.579  44.162   1.816  0.00  0.00      7
ATOM   1919  CA  ASN  245     14.114  45.189   0.959  0.00  0.00      6
ATOM   1920  CB  ASN  245     15.053  46.064   1.789  0.00  0.00      6
ATOM   1921  CG  ASN  245     15.593  47.246   1.019  0.00  0.00      6
ATOM   1922  OD1 ASN  245     15.664  47.219  -0.210  0.00  0.00      8
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FIG.23.28

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ATOM   1923  ND2 ASN   245      16.028  48.275   1.743  0.00  0.00      7
ATOM   1924  C   ASN   245      14.871  44.471  -0.180  0.00  0.00      6
ATOM   1925  O   ASN   245      15.938  43.878   0.019  0.00  0.00      8
ATOM   1926  N   ILE   246      14.309  44.560  -1.383  0.00  0.00      7
ATOM   1927  CA  ILE   246      14.888  43.913  -2.562  0.00  0.00      6
ATOM   1928  CB  ILE   246      13.872  43.930  -3.740  0.00  0.00      6
ATOM   1929  CG2 ILE   246      13.701  45.363  -4.312  0.00  0.00      6
ATOM   1930  CG1 ILE   246      14.306  42.918  -4.792  0.00  0.00      6
ATOM   1931  CD1 ILE   246      13.305  42.730  -5.875  0.00  0.00      6
ATOM   1932  C   ILE   246      16.261  44.428  -2.959  0.00  0.00      6
ATOM   1933  O   ILE   246      17.053  43.722  -3.580  0.00  0.00      8
ATOM   1934  N   TYR   247      16.575  45.652  -2.551  0.00  0.00      7
ATOM   1935  CA  TYR   247      17.875  46.252  -2.836  0.00  0.00      6
ATOM   1936  CB  TYR   247      17.789  47.780  -2.804  0.00  0.00      6
ATOM   1937  CG  TYR   247      17.100  48.426  -3.981  0.00  0.00      6
ATOM   1938  CD1 TYR   247      16.687  47.679  -5.079  0.00  0.00      6
ATOM   1939  CE1 TYR   247      16.107  48.291  -6.179  0.00  0.00      6
ATOM   1940  CD2 TYR   247      16.904  49.811  -4.023  0.00  0.00      6
ATOM   1941  CE2 TYR   247      16.335  50.421  -5.111  0.00  0.00      6
ATOM   1942  CZ  TYR   247      15.941  49.659  -6.189  0.00  0.00      6
ATOM   1943  OH  TYR   247      15.411  50.250  -7.306  0.00  0.00      8
ATOM   1944  C   TYR   247      18.969  45.831  -1.847  0.00  0.00      6
ATOM   1945  O   TYR   247      20.153  46.087  -2.056  0.00  0.00      8
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FIG.23.29

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ATOM  1946  N   ASN  248      18.584  45.227  -0.741  0.00  0.00      7
ATOM  1947  CA  ASN  248      19.579  44.834   0.241  0.00  0.00      6
ATOM  1948  CB  ASN  248      20.107  46.057   0.971  0.00  0.00      6
ATOM  1949  CG  ASN  248      21.294  45.739   1.824  0.00  0.00      6
ATOM  1950  OD1 ASN  248      21.349  44.701   2.461  0.00  0.00      8
ATOM  1951  ND2 ASN  248      22.273  46.610   1.812  0.00  0.00      7
ATOM  1952  C   ASN  248      18.827  43.940   1.178  0.00  0.00      6
ATOM  1953  O   ASN  248      17.964  44.401   1.916  0.00  0.00      8
ATOM  1954  N   LEU  249      19.094  42.645   1.091  0.00  0.00      7
ATOM  1955  CA  LEU  249      18.384  41.674   1.911  0.00  0.00      6
ATOM  1956  CB  LEU  249      18.824  40.251   1.503  0.00  0.00      6
ATOM  1957  CG  LEU  249      18.163  39.074   2.235  0.00  0.00      6
ATOM  1958  CD1 LEU  249      16.675  39.049   1.987  0.00  0.00      6
ATOM  1959  CD2 LEU  249      18.809  37.771   1.812  0.00  0.00      6
ATOM  1960  C   LEU  249      18.548  41.899   3.431  0.00  0.00      6
ATOM  1961  O   LEU  249      17.593  41.769   4.199  0.00  0.00      8
ATOM  1962  N   TYR  250      19.744  42.319   3.840  0.00  0.00      7
ATOM  1963  CA  TYR  250      20.070  42.499   5.249  0.00  0.00      6
ATOM  1964  CB  TYR  250      21.507  42.075   5.456  0.00  0.00      6
ATOM  1965  CG  TYR  250      21.696  40.673   4.951  0.00  0.00      6
ATOM  1966  CD1 TYR  250      22.611  40.392   3.942  0.00  0.00      6
ATOM  1967  CE1 TYR  250      22.736  39.107   3.417  0.00  0.00      6
ATOM  1968  CD2 TYR  250      20.906  39.636   5.435  0.00  0.00      6
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FIG.23.30

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ATOM  1969  CE2 TYR  250      21.026  38.333   4.915  0.00  0.00      6
ATOM  1970  CZ  TYR  250      21.950  38.070   3.901  0.00  0.00      6
ATOM  1971  OH  TYR  250      22.115  36.782   3.399  0.00  0.00      8
ATOM  1972  C   TYR  250      19.829  43.878   5.820  0.00  0.00      6
ATOM  1973  O   TYR  250      20.307  44.211   6.899  0.00  0.00      8
ATOM  1974  N   ALA  251      19.013  44.638   5.110  0.00  0.00      7
ATOM  1975  CA  ALA  251      18.682  45.978   5.504  0.00  0.00      6
ATOM  1976  CB  ALA  251      19.211  46.984   4.478  0.00  0.00      6
ATOM  1977  C   ALA  251      17.184  46.107   5.662  0.00  0.00      6
ATOM  1978  O   ALA  251      16.402  45.368   5.046  0.00  0.00      8
ATOM  1979  N   PRO  252      16.761  47.014   6.558  0.00  0.00      7
ATOM  1980  CD  PRO  252      17.590  47.925   7.376  0.00  0.00      6
ATOM  1981  CA  PRO  252      15.343  47.259   6.815  0.00  0.00      6
ATOM  1982  CB  PRO  252      15.382  48.209   8.018  0.00  0.00      6
ATOM  1983  CG  PRO  252      16.596  49.021   7.741  0.00  0.00      6
ATOM  1984  C   PRO  252      14.705  47.930   5.594  0.00  0.00      6
ATOM  1985  O   PRO  252      15.398  48.442   4.703  0.00  0.00      8
ATOM  1986  N   CYS  253      13.383  47.905   5.573  0.00  0.00      7
ATOM  1987  CA  CYS  253      12.599  48.492   4.523  0.00  0.00      6
ATOM  1988  C   CYS  253      12.128  49.812   5.106  0.00  0.00      6
ATOM  1989  O   CYS  253      11.530  49.824   6.180  0.00  0.00      8
ATOM  1990  CB  CYS  253      11.421  47.563   4.204  0.00  0.00      6
ATOM  1991  SG  CYS  253      10.314  48.110   2.865  0.00  0.00     16
```

FIG.23.31

ATOM	1992	N	ALA	254	12.481	50.919	4.451	0.00	0.00	7
ATOM	1993	CA	ALA	254	12.072	52.252	4.903	0.00	0.00	6
ATOM	1994	CB	ALA	254	12.501	53.319	3.913	0.00	0.00	6
ATOM	1995	C	ALA	254	10.561	52.278	5.090	0.00	0.00	6
ATOM	1996	O	ALA	254	9.808	52.014	4.148	0.00	0.00	8
ATOM	1997	N	GLY	255	10.122	52.568	6.312	0.00	0.00	7
ATOM	1998	CA	GLY	255	8.697	52.590	6.579	0.00	0.00	6
ATOM	1999	C	GLY	255	8.186	51.275	7.148	0.00	0.00	6
ATOM	2000	O	GLY	255	6.991	51.117	7.409	0.00	0.00	8
ATOM	2001	N	GLY	256	9.080	50.316	7.322	0.00	0.00	7
ATOM	2002	CA	GLY	256	8.672	49.051	7.887	0.00	0.00	6
ATOM	2003	C	GLY	256	7.810	48.165	7.016	0.00	0.00	6
ATOM	2004	O	GLY	256	7.610	48.417	5.825	0.00	0.00	8
ATOM	2005	N	VAL	257	7.334	47.088	7.632	0.00	0.00	7
ATOM	2006	CA	VAL	257	6.489	46.094	6.977	0.00	0.00	6
ATOM	2007	CB	VAL	257	6.907	44.664	7.384	0.00	0.00	6
ATOM	2008	CG1	VAL	257	5.968	43.641	6.791	0.00	0.00	6
ATOM	2009	CG2	VAL	257	8.318	44.394	6.934	0.00	0.00	6
ATOM	2010	C	VAL	257	5.026	46.323	7.346	0.00	0.00	6
ATOM	2011	O	VAL	257	4.678	46.411	8.535	0.00	0.00	8
ATOM	2012	N	PRO	258	4.165	46.487	6.325	0.00	0.00	7
ATOM	2013	CD	PRO	258	4.580	46.636	4.916	0.00	0.00	6
ATOM	2014	CA	PRO	258	2.721	46.716	6.470	0.00	0.00	6

FIG.23.32

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ATOM   2015  CB  PRO   258       2.297  47.095   5.048  0.00  0.00      6
ATOM   2016  CG  PRO   258       3.304  46.399   4.186  0.00  0.00      6
ATOM   2017  C   PRO   258       1.922  45.507   7.000  0.00  0.00      6
ATOM   2018  OT1 PRO   258       2.338  44.354   6.738  0.00  0.00      8
ATOM   2019  OT2 PRO   258       0.882  45.733   7.681  0.00  0.00      8
TER
ATOM   2020  CB  ALA   261      -0.009  50.908  -0.677  0.00  0.00      6
ATOM   2021  C   ALA   261       1.573  52.567   0.349  0.00  0.00      6
ATOM   2022  O   ALA   261       0.678  52.779   1.163  0.00  0.00      8
ATOM   2023  N   ALA   261       2.399  50.298  -0.348  0.00  0.00      7
ATOM   2024  CA  ALA   261       1.453  51.418  -0.640  0.00  0.00      6
ATOM   2025  N   ARG   262       2.680  53.297   0.309  0.00  0.00      7
ATOM   2026  CA  ARG   262       2.834  54.443   1.209  0.00  0.00      6
ATOM   2027  CB  ARG   262       4.240  55.067   1.099  0.00  0.00      6
ATOM   2028  CG  ARG   262       5.417  54.108   1.424  0.00  0.00      6
ATOM   2029  CD  ARG   262       6.775  54.691   0.940  0.00  0.00      6
ATOM   2030  NE  ARG   262       7.188  55.907   1.671  0.00  0.00      7
ATOM   2031  CZ  ARG   262       8.165  56.741   1.285  0.00  0.00      6
ATOM   2032  NH1 ARG   262       8.847  56.506   0.155  0.00  0.00      7
ATOM   2033  NH2 ARG   262       8.482  57.794   2.055  0.00  0.00      7
ATOM   2034  C   ARG   262       1.813  55.440   0.695  0.00  0.00      6
ATOM   2035  O   ARG   262       1.630  55.597  -0.512  0.00  0.00      8
ATOM   2036  N   ALA   263       1.070  56.036   1.605  0.00  0.00      7
```

FIG.23.33

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ATOM   2037  CA  ALA   263       0.080  57.022   1.205  0.00  0.00      6
ATOM   2038  CB  ALA   263      -1.296  56.693   1.798  0.00  0.00      6
ATOM   2039  C   ALA   263       0.630  58.295   1.802  0.00  0.00      6
ATOM   2040  O   ALA   263       1.264  58.265   2.881  0.00  0.00      8
ATOM   2041  N   GLU   264       0.472  59.398   1.081  0.00  0.00      7
ATOM   2042  CA  GLU   264       0.992  60.638   1.590  0.00  0.00      6
ATOM   2043  CB  GLU   264       2.256  61.005   0.831  0.00  0.00      6
ATOM   2044  CG  GLU   264       3.211  59.827   0.776  0.00  0.00      6
ATOM   2045  CD  GLU   264       4.656  60.243   0.654  0.00  0.00      6
ATOM   2046  OE1 GLU   264       4.923  61.325   0.053  0.00  0.00      8
ATOM   2047  OE2 GLU   264       5.528  59.485   1.175  0.00  0.00      8
ATOM   2048  C   GLU   264      -0.054  61.735   1.542  0.00  0.00      6
ATOM   2049  O   GLU   264       0.290  62.938   1.510  0.00  0.00      8
ATOM   2050  N   ALA   265      -1.319  61.309   1.657  0.00  0.00      7
ATOM   2051  CA  ALA   265      -2.479  62.210   1.643  0.00  0.00      6
ATOM   2052  CB  ALA   265      -2.304  63.354   2.656  0.00  0.00      6
ATOM   2053  C   ALA   265      -2.674  62.761   0.244  0.00  0.00      6
ATOM   2054  O   ALA   265      -2.042  63.746  -0.147  0.00  0.00      8
ATOM   2055  N   ASP   266      -3.558  62.096  -0.493  0.00  0.00      7
ATOM   2056  CA  ASP   266      -3.858  62.447  -1.875  0.00  0.00      6
ATOM   2057  CB  ASP   266      -4.058  63.957  -2.035  0.00  0.00      6
ATOM   2058  CG  ASP   266      -5.223  64.479  -1.208  0.00  0.00      6
ATOM   2059  OD1 ASP   266      -5.856  63.689  -0.455  0.00  0.00      8
```

FIG.23.34

ATOM	2060	OD2	ASP	266	-5.510	65.689	-1.321	0.00	0.00	8
ATOM	2061	C	ASP	266	-2.747	61.960	-2.792	0.00	0.00	6
ATOM	2062	O	ASP	266	-2.685	62.352	-3.953	0.00	0.00	8
ATOM	2063	N	THR	267	-1.888	61.090	-2.263	0.00	0.00	7
ATOM	2064	CA	THR	267	-0.780	60.535	-3.026	0.00	0.00	6
ATOM	2065	CB	THR	267	0.565	61.234	-2.730	0.00	0.00	6
ATOM	2066	OG1	THR	267	0.547	62.571	-3.246	0.00	0.00	8
ATOM	2067	CG2	THR	267	1.714	60.471	-3.377	0.00	0.00	6
ATOM	2068	C	THR	267	-0.589	59.090	-2.657	0.00	0.00	6
ATOM	2069	O	THR	267	-0.277	58.775	-1.500	0.00	0.00	8
ATOM	2070	N	VAL	268	-0.807	58.218	-3.634	0.00	0.00	7
ATOM	2071	CA	VAL	268	-0.604	56.789	-3.451	0.00	0.00	6
ATOM	2072	CB	VAL	268	-1.566	55.980	-4.329	0.00	0.00	6
ATOM	2073	CG1	VAL	268	-1.153	54.535	-4.362	0.00	0.00	6
ATOM	2074	CG2	VAL	268	-2.961	56.107	-3.796	0.00	0.00	6
ATOM	2075	C	VAL	268	0.823	56.557	-3.919	0.00	0.00	6
ATOM	2076	O	VAL	268	1.207	57.046	-4.980	0.00	0.00	8
ATOM	2077	N	VAL	269	1.635	55.897	-3.110	0.00	0.00	7
ATOM	2078	CA	VAL	269	3.006	55.649	-3.512	0.00	0.00	6
ATOM	2079	CB	VAL	269	4.025	55.941	-2.375	0.00	0.00	6
ATOM	2080	CG1	VAL	269	5.437	55.724	-2.860	0.00	0.00	6
ATOM	2081	CG2	VAL	269	3.894	57.366	-1.913	0.00	0.00	6
ATOM	2082	C	VAL	269	3.088	54.196	-3.961	0.00	0.00	6

FIG.23.35

ATOM	2083	O	VAL	269	2.609	53.294	-3.279	0.00	0.00	8
ATOM	2084	N	VAL	270	3.634	53.987	-5.150	0.00	0.00	7
ATOM	2085	CA	VAL	270	3.784	52.660	-5.733	0.00	0.00	6
ATOM	2086	CB	VAL	270	3.143	52.594	-7.155	0.00	0.00	6
ATOM	2087	CG1	VAL	270	3.578	51.343	-7.884	0.00	0.00	6
ATOM	2088	CG2	VAL	270	1.634	52.596	-7.022	0.00	0.00	6
ATOM	2089	C	VAL	270	5.274	52.440	-5.804	0.00	0.00	6
ATOM	2090	O	VAL	270	6.017	53.391	-6.003	0.00	0.00	8
ATOM	2091	N	GLN	271	5.718	51.204	-5.597	0.00	0.00	7
ATOM	2092	CA	GLN	271	7.152	50.896	-5.613	0.00	0.00	6
ATOM	2093	CB	GLN	271	7.621	50.532	-4.204	0.00	0.00	6
ATOM	2094	CG	GLN	271	7.301	51.578	-3.157	0.00	0.00	6
ATOM	2095	CD	GLN	271	8.131	51.420	-1.877	0.00	0.00	6
ATOM	2096	OE1	GLN	271	8.438	50.290	-1.443	0.00	0.00	8
ATOM	2097	NE2	GLN	271	8.516	52.559	-1.273	0.00	0.00	7
ATOM	2098	C	GLN	271	7.534	49.769	-6.575	0.00	0.00	6
ATOM	2099	O	GLN	271	8.579	49.168	-6.416	0.00	0.00	8
ATOM	2100	N	ASP	272	6.741	49.553	-7.621	0.00	0.00	7
ATOM	2101	CA	ASP	272	6.991	48.479	-8.573	0.00	0.00	6
ATOM	2102	CB	ASP	272	5.663	47.737	-8.815	0.00	0.00	6
ATOM	2103	CG	ASP	272	5.785	46.584	-9.784	0.00	0.00	6
ATOM	2104	OD1	ASP	272	6.887	46.018	-9.923	0.00	0.00	8
ATOM	2105	OD2	ASP	272	4.765	46.252	-10.414	0.00	0.00	8

FIG.23.36

```
ATOM   2106  C   ASP  272      7.602  49.000  -9.875  0.00  0.00      6
ATOM   2107  O   ASP  272      6.895  49.474 -10.753  0.00  0.00      8
ATOM   2108  N   LEU  273      8.918  48.904  -9.999  0.00  0.00      7
ATOM   2109  CA  LEU  273      9.605  49.376 -11.188  0.00  0.00      6
ATOM   2110  CB  LEU  273     11.085  49.625 -10.894  0.00  0.00      6
ATOM   2111  CG  LEU  273     11.446  50.578  -9.748  0.00  0.00      6
ATOM   2112  CD1 LEU  273     12.895  50.870  -9.815  0.00  0.00      6
ATOM   2113  CD2 LEU  273     10.703  51.843  -9.826  0.00  0.00      6
ATOM   2114  C   LEU  273      9.426  48.467 -12.416  0.00  0.00      6
ATOM   2115  O   LEU  273      9.729  48.883 -13.533  0.00  0.00      8
ATOM   2116  N   GLY  274      8.984  47.224 -12.192  0.00  0.00      7
ATOM   2117  CA  GLY  274      8.713  46.269 -13.268  0.00  0.00      6
ATOM   2118  C   GLY  274      9.830  45.462 -13.913  0.00  0.00      6
ATOM   2119  O   GLY  274      9.643  44.975 -15.019  0.00  0.00      8
ATOM   2120  N   ASN  275     10.923  45.207 -13.198  0.00  0.00      7
ATOM   2121  CA  ASN  275     12.031  44.497 -13.795  0.00  0.00      6
ATOM   2122  CB  ASN  275     13.296  45.296 -13.626  0.00  0.00      6
ATOM   2123  CG  ASN  275     13.164  46.690 -14.162  0.00  0.00      6
ATOM   2124  OD1 ASN  275     12.778  46.902 -15.309  0.00  0.00      8
ATOM   2125  ND2 ASN  275     13.461  47.664 -13.319  0.00  0.00      7
ATOM   2126  C   ASN  275     12.327  43.048 -13.447  0.00  0.00      6
ATOM   2127  O   ASN  275     13.267  42.486 -14.001  0.00  0.00      8
ATOM   2128  N   ILE  276     11.584  42.434 -12.531  0.00  0.00      7
```

FIG.23.37

ATOM	2129	CA	ILE	276	11.866	41.036	-12.189	0.00	0.00	6
ATOM	2130	CB	ILE	276	12.317	40.809	-10.687	0.00	0.00	6
ATOM	2131	CG2	ILE	276	13.643	41.508	-10.400	0.00	0.00	6
ATOM	2132	CG1	ILE	276	11.238	41.267	-9.707	0.00	0.00	6
ATOM	2133	CD1	ILE	276	11.518	40.911	-8.245	0.00	0.00	6
ATOM	2134	C	ILE	276	10.665	40.170	-12.511	0.00	0.00	6
ATOM	2135	O	ILE	276	9.538	40.653	-12.467	0.00	0.00	8
ATOM	2136	N	PHE	277	10.922	38.906	-12.864	0.00	0.00	7
ATOM	2137	CA	PHE	277	9.879	37.931	-13.204	0.00	0.00	6
ATOM	2138	CB	PHE	277	9.151	37.436	-11.942	0.00	0.00	6
ATOM	2139	CG	PHE	277	10.048	36.692	-10.993	0.00	0.00	6
ATOM	2140	CD1	PHE	277	10.279	37.179	-9.702	0.00	0.00	6
ATOM	2141	CD2	PHE	277	10.728	35.559	-11.418	0.00	0.00	6
ATOM	2142	CE1	PHE	277	11.186	36.548	-8.852	0.00	0.00	6
ATOM	2143	CE2	PHE	277	11.631	34.921	-10.582	0.00	0.00	6
ATOM	2144	CZ	PHE	277	11.867	35.416	-9.293	0.00	0.00	6
ATOM	2145	C	PHE	277	8.901	38.441	-14.243	0.00	0.00	6
ATOM	2146	O	PHE	277	7.708	38.176	-14.161	0.00	0.00	8
ATOM	2147	N	THR	278	9.442	39.166	-15.226	0.00	0.00	7
ATOM	2148	CA	THR	278	8.675	39.768	-16.329	0.00	0.00	6
ATOM	2149	CB	THR	278	9.578	40.666	-17.194	0.00	0.00	6
ATOM	2150	OG1	THR	278	10.712	39.911	-17.634	0.00	0.00	8
ATOM	2151	CG2	THR	278	10.074	41.888	-16.402	0.00	0.00	6

FIG.23.38

```
ATOM   2152  C   THR   278      7.972  38.737  -17.243  0.00  0.00      6
ATOM   2153  O   THR   278      7.034  39.085  -17.974  0.00  0.00      8
ATOM   2154  N   ARG   279      8.417  37.479  -17.190  0.00  0.00      7
ATOM   2155  CA  ARG   279      7.806  36.427  -17.993  0.00  0.00      6
ATOM   2156  CB  ARG   279      8.866  35.601  -18.722  0.00  0.00      6
ATOM   2157  CG  ARG   279      9.494  36.345  -19.885  0.00  0.00      6
ATOM   2158  CD  ARG   279      8.441  36.813  -20.862  0.00  0.00      6
ATOM   2159  NE  ARG   279      8.996  37.816  -21.751  0.00  0.00      7
ATOM   2160  CZ  ARG   279      8.445  39.006  -21.991  0.00  0.00      6
ATOM   2161  NH1 ARG   279      7.298  39.359  -21.411  0.00  0.00      7
ATOM   2162  NH2 ARG   279      9.071  39.868  -22.783  0.00  0.00      7
ATOM   2163  C   ARG   279      6.786  35.544  -17.273  0.00  0.00      6
ATOM   2164  O   ARG   279      6.447  34.465  -17.746  0.00  0.00      8
ATOM   2165  N   LEU   280      6.281  36.025  -16.142  0.00  0.00      7
ATOM   2166  CA  LEU   280      5.255  35.316  -15.377  0.00  0.00      6
ATOM   2167  CB  LEU   280      5.489  35.460  -13.865  0.00  0.00      6
ATOM   2168  CG  LEU   280      6.707  34.768  -13.261  0.00  0.00      6
ATOM   2169  CD1 LEU   280      6.719  35.031  -11.789  0.00  0.00      6
ATOM   2170  CD2 LEU   280      6.660  33.273  -13.532  0.00  0.00      6
ATOM   2171  C   LEU   280      3.966  35.998  -15.784  0.00  0.00      6
ATOM   2172  O   LEU   280      4.011  37.021  -16.462  0.00  0.00      8
ATOM   2173  N   PRO   281      2.797  35.448  -15.407  0.00  0.00      7
ATOM   2174  CD  PRO   281      2.533  34.197  -14.683  0.00  0.00      6
```

FIG.23.39

```
ATOM   2175  CA  PRO   281       1.538  36.091 -15.788  0.00  0.00      6
ATOM   2176  CB  PRO   281       0.494  35.250 -15.076  0.00  0.00      6
ATOM   2177  CG  PRO   281       1.112  33.894 -15.107  0.00  0.00      6
ATOM   2178  C   PRO   281       1.508  37.523 -15.301  0.00  0.00      6
ATOM   2179  O   PRO   281       2.003  37.825 -14.214  0.00  0.00      8
ATOM   2180  N   LEU   282       0.935  38.386 -16.139  0.00  0.00      7
ATOM   2181  CA  LEU   282       0.803  39.818 -15.906  0.00  0.00      6
ATOM   2182  CB  LEU   282      -0.253  40.380 -16.862  0.00  0.00      6
ATOM   2183  CG  LEU   282      -0.631  41.845 -16.721  0.00  0.00      6
ATOM   2184  CD1 LEU   282       0.574  42.689 -16.995  0.00  0.00      6
ATOM   2185  CD2 LEU   282      -1.719  42.162 -17.691  0.00  0.00      6
ATOM   2186  C   LEU   282       0.398  40.150 -14.486  0.00  0.00      6
ATOM   2187  O   LEU   282      -0.581  39.608 -13.971  0.00  0.00      8
ATOM   2188  N   ALA   283       1.167  41.032 -13.857  0.00  0.00      7
ATOM   2189  CA  ALA   283       0.867  41.482 -12.503  0.00  0.00      6
ATOM   2190  CB  ALA   283       1.496  40.554 -11.459  0.00  0.00      6
ATOM   2191  C   ALA   283       1.391  42.908 -12.340  0.00  0.00      6
ATOM   2192  O   ALA   283       2.578  43.165 -12.503  0.00  0.00      8
ATOM   2193  N   ARG   284       0.492  43.836 -12.041  0.00  0.00      7
ATOM   2194  CA  ARG   284       0.871  45.224 -11.857  0.00  0.00      6
ATOM   2195  CB  ARG   284       0.221  46.106 -12.931  0.00  0.00      6
ATOM   2196  CG  ARG   284       0.543  45.713 -14.364  0.00  0.00      6
```

FIG.23.40

```
ATOM   2197  CD  ARG   284      1.989  46.015 -14.683  0.00  0.00      6
ATOM   2198  NE  ARG   284      2.326  45.745 -16.074  0.00  0.00      7
ATOM   2199  CZ  ARG   284      3.559  45.493 -16.497  0.00  0.00      6
ATOM   2200 NH1  ARG   284      4.578  45.465 -15.643  0.00  0.00      7
ATOM   2201 NH2  ARG   284      3.786  45.297 -17.781  0.00  0.00      7
ATOM   2202   C  ARG   284      0.338  45.627 -10.497  0.00  0.00      6
ATOM   2203   O  ARG   284     -0.867  45.520 -10.225  0.00  0.00      8
ATOM   2204   N  MET   285      1.237  46.089  -9.643  0.00  0.00      7
ATOM   2205  CA  MET   285      0.847  46.529  -8.308  0.00  0.00      6
ATOM   2206  CB  MET   285      2.087  46.868  -7.469  0.00  0.00      6
ATOM   2207  CG  MET   285      2.904  45.652  -7.037  0.00  0.00      6
ATOM   2208  SD  MET   285      1.890  44.362  -6.271  0.00  0.00     16
ATOM   2209  CE  MET   285      1.602  45.101  -4.693  0.00  0.00      6
ATOM   2210   C  MET   285     -0.123  47.722  -8.341  0.00  0.00      6
ATOM   2211   O  MET   285     -1.108  47.753  -7.594  0.00  0.00      8
ATOM   2212   N  TRP   286      0.123  48.676  -9.238  0.00  0.00      7
ATOM   2213  CA  TRP   286     -0.742  49.846  -9.313  0.00  0.00      6
ATOM   2214  CB  TRP   286     -0.219  50.882 -10.323  0.00  0.00      6
ATOM   2215  CG  TRP   286     -0.431  50.530 -11.769  0.00  0.00      6
ATOM   2216 CD2  TRP   286     -1.598  50.813 -12.556  0.00  0.00      6
ATOM   2217 CE2  TRP   286     -1.347  50.335 -13.869  0.00  0.00      6
ATOM   2218 CE3  TRP   286     -2.831  51.424 -12.282  0.00  0.00      6
ATOM   2219 CD1  TRP   286      0.461  49.900 -12.617  0.00  0.00      6
```

FIG.23.41

```
ATOM   2220  NE1 TRP   286      -0.090  49.784 -13.876   0.00   0.00      7
ATOM   2221  CZ2 TRP   286      -2.293  50.457 -14.907   0.00   0.00      6
ATOM   2222  CZ3 TRP   286      -3.772  51.538 -13.308   0.00   0.00      6
ATOM   2223  CH2 TRP   286      -3.494  51.057 -14.606   0.00   0.00      6
ATOM   2224  C   TRP   286      -2.192  49.488  -9.612   0.00   0.00      6
ATOM   2225  O   TRP   286      -3.085  50.273  -9.292   0.00   0.00      8
ATOM   2226  N   HIS   287      -2.441  48.309 -10.188   0.00   0.00      7
ATOM   2227  CA  HIS   287      -3.811  47.900 -10.509   0.00   0.00      6
ATOM   2228  CB  HIS   287      -3.834  46.532 -11.209   0.00   0.00      6
ATOM   2229  CG  HIS   287      -3.407  46.561 -12.647   0.00   0.00      6
ATOM   2230  CD2 HIS   287      -3.198  47.590 -13.506   0.00   0.00      6
ATOM   2231  ND1 HIS   287      -3.106  45.416 -13.353   0.00   0.00      7
ATOM   2232  CE1 HIS   287      -2.718  45.738 -14.575   0.00   0.00      6
ATOM   2233  NE2 HIS   287      -2.767  47.050 -14.693   0.00   0.00      7
ATOM   2234  C   HIS   287      -4.650  47.811  -9.234   0.00   0.00      6
ATOM   2235  O   HIS   287      -5.878  47.944  -9.264   0.00   0.00      8
ATOM   2236  N   GLN   288      -3.967  47.577  -8.117   0.00   0.00      7
ATOM   2237  CA  GLN   288      -4.610  47.443  -6.802   0.00   0.00      6
ATOM   2238  CB  GLN   288      -3.701  46.642  -5.862   0.00   0.00      6
ATOM   2239  CG  GLN   288      -3.478  45.210  -6.320   0.00   0.00      6
ATOM   2240  CD  GLN   288      -2.388  44.516  -5.543   0.00   0.00      6
ATOM   2241  OE1 GLN   288      -1.497  43.898  -6.132   0.00   0.00      8
ATOM   2242  NE2 GLN   288      -2.434  44.622  -4.214   0.00   0.00      7
```

FIG.23.42

ATOM	2243	C	GLN	288	-4.978	48.777	-6.157	0.00	0.00	6	
ATOM	2244	O	GLN	288	-5.824	48.838	-5.266	0.00	0.00	8	
ATOM	2283	N	GLY	294	-8.616	62.996	-7.864	0.00	0.00	7	
ATOM	2284	CA	GLY	294	-7.718	64.021	-7.349	0.00	0.00	6	
ATOM	2285	C	GLY	294	-6.522	63.501	-6.557	0.00	0.00	6	
ATOM	2286	O	GLY	294	-5.796	64.272	-5.930	0.00	0.00	8	
ATOM	2287	N	ASP	295	-6.368	62.187	-6.508	0.00	0.00	7	
ATOM	2288	CA	ASP	295	-5.239	61.593	-5.828	0.00	0.00	6	
ATOM	2289	CB	ASP	295	-5.606	60.232	-5.239	0.00	0.00	6	
ATOM	2290	CG	ASP	295	-6.281	60.339	-3.884	0.00	0.00	6	
ATOM	2291	OD1	ASP	295	-6.508	61.465	-3.386	0.00	0.00	8	
ATOM	2292	OD2	ASP	295	-6.583	59.269	-3.313	0.00	0.00	8	
ATOM	2293	C	ASP	295	-4.219	61.398	-6.918	0.00	0.00	6	
ATOM	2294	O	ASP	295	-4.566	61.211	-8.084	0.00	0.00	8	
ATOM	2295	N	ALA	296	-2.956	61.491	-6.558	0.00	0.00	7	
ATOM	2296	CA	ALA	296	-1.899	61.296	-7.521	0.00	0.00	6	
ATOM	2297	CB	ALA	296	-0.972	62.464	-7.509	0.00	0.00	6	
ATOM	2298	C	ALA	296	-1.148	60.046	-7.129	0.00	0.00	6	
ATOM	2299	O	ALA	296	-1.077	59.684	-5.944	0.00	0.00	8	
ATOM	2300	N	VAL	297	-0.606	59.377	-8.134	0.00	0.00	7	
ATOM	2301	CA	VAL	297	0.168	58.178	-7.907	0.00	0.00	6	
ATOM	2302	CB	VAL	297	-0.226	57.053	-8.891	0.00	0.00	6	

FIG.23.43

```
ATOM   2303  CG1 VAL   297       0.648  55.834  -8.686  0.00  0.00      6
ATOM   2304  CG2 VAL   297      -1.655  56.686  -8.709  0.00  0.00      6
ATOM   2305  C   VAL   297       1.618  58.558  -8.157  0.00  0.00      6
ATOM   2306  O   VAL   297       1.938  59.111  -9.233  0.00  0.00      8
ATOM   2307  N   ARG   298       2.466  58.375  -7.140  0.00  0.00      7
ATOM   2308  CA  ARG   298       3.887  58.647  -7.278  0.00  0.00      6
ATOM   2309  CB  ARG   298       4.404  59.591  -6.203  0.00  0.00      6
ATOM   2310  CG  ARG   298       5.916  59.827  -6.337  0.00  0.00      6
ATOM   2311  CD  ARG   298       6.491  60.782  -5.309  0.00  0.00      6
ATOM   2312  NE  ARG   298       6.961  60.120  -4.094  0.00  0.00      7
ATOM   2313  CZ  ARG   298       6.335  60.172  -2.919  0.00  0.00      6
ATOM   2314  NH1 ARG   298       5.207  60.866  -2.796  0.00  0.00      7
ATOM   2315  NH2 ARG   298       6.818  59.505  -1.870  0.00  0.00      7
ATOM   2316  C   ARG   298       4.601  57.304  -7.153  0.00  0.00      6
ATOM   2317  O   ARG   298       4.235  56.488  -6.312  0.00  0.00      8
ATOM   2318  N   MET   299       5.615  57.074  -7.975  0.00  0.00      7
ATOM   2319  CA  MET   299       6.350  55.831  -7.920  0.00  0.00      6
ATOM   2320  CB  MET   299       6.558  55.267  -9.327  0.00  0.00      6
ATOM   2321  CG  MET   299       7.262  53.919  -9.359  0.00  0.00      6
ATOM   2322  SD  MET   299       7.645  53.364 -11.007  0.00  0.00     16
ATOM   2323  CE  MET   299       9.150  54.215 -11.342  0.00  0.00      6
ATOM   2324  C   MET   299       7.703  56.079  -7.290  0.00  0.00      6
ATOM   2325  O   MET   299       8.433  56.971  -7.733  0.00  0.00      8
```

FIG.23.44

```
ATOM   2326  N   ASP   300      8.056  55.275  -6.290  0.00  0.00      7
ATOM   2327  CA  ASP   300      9.343  55.404  -5.613  0.00  0.00      6
ATOM   2328  CB  ASP   300      9.158  55.690  -4.126  0.00  0.00      6
ATOM   2329  CG  ASP   300      8.716  57.098  -3.835  0.00  0.00      6
ATOM   2330  OD1 ASP   300      8.569  57.929  -4.760  0.00  0.00      8
ATOM   2331  OD2 ASP   300      8.502  57.364  -2.642  0.00  0.00      8
ATOM   2332  C   ASP   300     10.068  54.086  -5.687  0.00  0.00      6
ATOM   2333  O   ASP   300      9.455  53.051  -5.864  0.00  0.00      8
ATOM   2334  N   PRO   301     11.394  54.108  -5.534  0.00  0.00      7
ATOM   2335  CD  PRO   301     12.291  55.278  -5.447  0.00  0.00      6
ATOM   2336  CA  PRO   301     12.145  52.849  -5.568  0.00  0.00      6
ATOM   2337  CB  PRO   301     13.584  53.315  -5.385  0.00  0.00      6
ATOM   2338  CG  PRO   301     13.563  54.734  -5.991  0.00  0.00      6
ATOM   2339  C   PRO   301     11.672  51.992  -4.371  0.00  0.00      6
ATOM   2340  O   PRO   301     11.280  52.520  -3.319  0.00  0.00      8
ATOM   2341  N   PRO   302     11.703  50.671  -4.507  0.00  0.00      7
ATOM   2342  CD  PRO   302     12.233  49.843  -5.589  0.00  0.00      6
ATOM   2343  CA  PRO   302     11.259  49.818  -3.412  0.00  0.00      6
ATOM   2344  CB  PRO   302     11.429  48.427  -4.005  0.00  0.00      6
ATOM   2345  CG  PRO   302     12.588  48.584  -4.852  0.00  0.00      6
ATOM   2346  C   PRO   302     12.022  49.981  -2.103  0.00  0.00      6
ATOM   2347  O   PRO   302     13.262  50.022  -2.084  0.00  0.00      8
ATOM   2348  N   CYS   303     11.250  50.124  -1.022  0.00  0.00      7
```

FIG.23.45

```
ATOM   2349  CA  CYS   303      11.781  50.260   0.334  0.00  0.00      6
ATOM   2350  C   CYS   303      12.739  51.391   0.542  0.00  0.00      6
ATOM   2351  O   CYS   303      13.597  51.309   1.404  0.00  0.00      8
ATOM   2352  CB  CYS   303      12.453  48.965   0.797  0.00  0.00      6
ATOM   2353  SG  CYS   303      11.287  47.610   1.151  0.00  0.00     16
ATOM   2354  N   THR   304      12.602  52.440  -0.264  0.00  0.00      7
ATOM   2355  CA  THR   304      13.447  53.618  -0.167  0.00  0.00      6
ATOM   2356  CB  THR   304      14.140  53.967  -1.499  0.00  0.00      6
ATOM   2357  OG1 THR   304      13.162  54.438  -2.432  0.00  0.00      8
ATOM   2358  CG2 THR   304      14.859  52.765  -2.070  0.00  0.00      6
ATOM   2359  C   THR   304      12.571  54.792   0.243  0.00  0.00      6
ATOM   2360  O   THR   304      11.354  54.802   0.008  0.00  0.00      8
ATOM   2361  N   ASN   305      13.210  55.764   0.878  0.00  0.00      7
ATOM   2362  CA  ASN   305      12.552  56.962   1.334  0.00  0.00      6
ATOM   2363  CB  ASN   305      12.859  57.170   2.814  0.00  0.00      6
ATOM   2364  CG  ASN   305      12.016  58.235   3.414  0.00  0.00      6
ATOM   2365  OD1 ASN   305      11.397  59.008   2.692  0.00  0.00      8
ATOM   2366  ND2 ASN   305      11.963  58.295   4.733  0.00  0.00      7
ATOM   2367  C   ASN   305      13.159  58.079   0.487  0.00  0.00      6
ATOM   2368  O   ASN   305      14.365  58.272   0.509  0.00  0.00      8
ATOM   2369  N   THR   306      12.341  58.782  -0.293  0.00  0.00      7
ATOM   2370  CA  THR   306      12.859  59.841  -1.151  0.00  0.00      6
ATOM   2371  CB  THR   306      12.269  59.700  -2.555  0.00  0.00      6
```

FIG.23.46

ATOM	2372	OG1	THR	306	10.835	59.751	-2.473	0.00	0.00	8
ATOM	2373	CG2	THR	306	12.722	58.357	-3.180	0.00	0.00	6
ATOM	2374	C	THR	306	12.662	61.272	-0.628	0.00	0.00	6
ATOM	2375	O	THR	306	13.099	62.243	-1.244	0.00	0.00	8
ATOM	2376	N	THR	307	12.058	61.382	0.542	0.00	0.00	7
ATOM	2377	CA	THR	307	11.796	62.662	1.166	0.00	0.00	6
ATOM	2378	CB	THR	307	11.210	62.436	2.554	0.00	0.00	6
ATOM	2379	OG1	THR	307	10.097	61.536	2.456	0.00	0.00	8
ATOM	2380	CG2	THR	307	10.778	63.768	3.181	0.00	0.00	6
ATOM	2381	C	THR	307	12.971	63.629	1.295	0.00	0.00	6
ATOM	2382	O	THR	307	12.829	64.792	0.982	0.00	0.00	8
ATOM	2383	N	ALA	308	14.125	63.186	1.772	0.00	0.00	7
ATOM	2384	CA	ALA	308	15.238	64.114	1.930	0.00	0.00	6
ATOM	2385	CB	ALA	308	16.418	63.443	2.620	0.00	0.00	6
ATOM	2386	C	ALA	308	15.677	64.725	0.604	0.00	0.00	6
ATOM	2387	O	ALA	308	15.855	65.931	0.504	0.00	0.00	8
ATOM	2388	N	ALA	309	15.821	63.894	-0.422	0.00	0.00	7
ATOM	2389	CA	ALA	309	16.253	64.367	-1.734	0.00	0.00	6
ATOM	2390	CB	ALA	309	16.610	63.166	-2.613	0.00	0.00	6
ATOM	2391	C	ALA	309	15.194	65.247	-2.420	0.00	0.00	6
ATOM	2392	O	ALA	309	15.485	66.306	-2.963	0.00	0.00	8
ATOM	2529	N	GLN	327	8.486	76.823	-14.820	0.00	0.00	7

FIG.23.47

```
ATOM   2530  CA  GLN   327      7.270  76.141 -15.206  0.00  0.00      6
ATOM   2531  CB  GLN   327      6.891  76.509 -16.641  0.00  0.00      6
ATOM   2532  CG  GLN   327      7.559  75.650 -17.725  0.00  0.00      6
ATOM   2533  CD  GLN   327      8.914  76.160 -18.181  0.00  0.00      6
ATOM   2534 OE1 GLN   327      9.580  75.503 -18.991  0.00  0.00      8
ATOM   2535 NE2 GLN   327      9.326  77.335 -17.684  0.00  0.00      7
ATOM   2536  C   GLN   327      7.326  74.624 -15.044  0.00  0.00      6
ATOM   2537  O   GLN   327      6.289  73.955 -15.084  0.00  0.00      8
ATOM   2538  N   LEU   328      8.525  74.080 -14.861  0.00  0.00      7
ATOM   2539  CA  LEU   328      8.679  72.642 -14.728  0.00  0.00      6
ATOM   2540  CB  LEU   328     10.159  72.240 -14.772  0.00  0.00      6
ATOM   2541  CG  LEU   328     10.805  72.604 -16.108  0.00  0.00      6
ATOM   2542 CD1 LEU   328     12.081  71.896 -16.233  0.00  0.00      6
ATOM   2543 CD2 LEU   328      9.906  72.211 -17.256  0.00  0.00      6
ATOM   2544  C   LEU   328      8.001  72.104 -13.487  0.00  0.00      6
ATOM   2545  O   LEU   328      7.967  72.758 -12.449  0.00  0.00      8
ATOM   2546  N   PRO   329      7.402  70.902 -13.593  0.00  0.00      7
ATOM   2547  CD  PRO   329      7.290  70.086 -14.813  0.00  0.00      6
ATOM   2548  CA  PRO   329      6.705  70.251 -12.477  0.00  0.00      6
ATOM   2549  CB  PRO   329      6.110  68.992 -13.115  0.00  0.00      6
ATOM   2550  CG  PRO   329      6.016  69.344 -14.565  0.00  0.00      6
ATOM   2551  C   PRO   329      7.673  69.894 -11.351  0.00  0.00      6
ATOM   2552  O   PRO   329      8.902  69.995 -11.480  0.00  0.00      8
```

FIG.23.48

ATOM	2553	N	GLN	330	7.093	69.415	-10.264	0.00	0.00	7
ATOM	2554	CA	GLN	330	7.835	69.066	-9.071	0.00	0.00	6
ATOM	2555	CB	GLN	330	6.808	68.680	-8.004	0.00	0.00	6
ATOM	2556	CG	GLN	330	7.319	67.845	-6.870	0.00	0.00	6
ATOM	2557	CD	GLN	330	6.188	67.187	-6.123	0.00	0.00	6
ATOM	2558	OE1	GLN	330	5.065	67.674	-6.135	0.00	0.00	8
ATOM	2559	NE2	GLN	330	6.471	66.055	-5.491	0.00	0.00	7
ATOM	2560	C	GLN	330	8.810	67.932	-9.348	0.00	0.00	6
ATOM	2561	O	GLN	330	8.546	67.069	-10.186	0.00	0.00	8
ATOM	2562	N	TRP	331	9.958	67.960	-8.686	0.00	0.00	7
ATOM	2563	CA	TRP	331	10.914	66.901	-8.848	0.00	0.00	6
ATOM	2564	CB	TRP	331	12.297	67.359	-8.387	0.00	0.00	6
ATOM	2565	CG	TRP	331	13.395	66.349	-8.625	0.00	0.00	6
ATOM	2566	CD2	TRP	331	13.827	65.291	-7.729	0.00	0.00	6
ATOM	2567	CE2	TRP	331	14.870	64.602	-8.374	0.00	0.00	6
ATOM	2568	CE3	TRP	331	13.429	64.870	-6.442	0.00	0.00	6
ATOM	2569	CD1	TRP	331	14.183	66.253	-9.729	0.00	0.00	6
ATOM	2570	NE1	TRP	331	15.071	65.215	-9.585	0.00	0.00	7
ATOM	2571	CZ2	TRP	331	15.537	63.504	-7.783	0.00	0.00	6
ATOM	2572	CZ3	TRP	331	14.091	63.776	-5.852	0.00	0.00	6
ATOM	2573	CH2	TRP	331	15.136	63.112	-6.527	0.00	0.00	6
ATOM	2574	C	TRP	331	10.466	65.684	-8.018	0.00	0.00	6
ATOM	2575	O	TRP	331	9.923	65.818	-6.917	0.00	0.00	8

FIG.23.49

```
ATOM   2576  N   ASP  332      10.642  64.501  -8.603  0.00  0.00      7
ATOM   2577  CA  ASP  332      10.349  63.200  -7.969  0.00  0.00      6
ATOM   2578  CB  ASP  332       9.084  62.538  -8.515  0.00  0.00      6
ATOM   2579  CG  ASP  332       7.858  63.322  -8.214  0.00  0.00      6
ATOM   2580  OD1 ASP  332       7.767  63.875  -7.097  0.00  0.00      8
ATOM   2581  OD2 ASP  332       6.984  63.367  -9.102  0.00  0.00      8
ATOM   2582  C   ASP  332      11.527  62.334  -8.349  0.00  0.00      6
ATOM   2583  O   ASP  332      12.108  62.512  -9.424  0.00  0.00      8
ATOM   2584  N   MET  333      11.921  61.416  -7.487  0.00  0.00      7
ATOM   2585  CA  MET  333      13.049  60.609  -7.887  0.00  0.00      6
ATOM   2586  CB  MET  333      13.614  59.802  -6.735  0.00  0.00      6
ATOM   2587  CG  MET  333      15.038  59.439  -7.018  0.00  0.00      6
ATOM   2588  SD  MET  333      15.679  58.885  -5.560  0.00  0.00     16
ATOM   2589  CE  MET  333      16.287  60.400  -4.882  0.00  0.00      6
ATOM   2590  C   MET  333      12.753  59.701  -9.079  0.00  0.00      6
ATOM   2591  O   MET  333      13.665  59.342  -9.815  0.00  0.00      8
ATOM   2592  N   CYS  334      11.478  59.371  -9.270  0.00  0.00      7
ATOM   2593  CA  CYS  334      11.026  58.513 -10.367  0.00  0.00      6
ATOM   2594  C   CYS  334       9.702  59.029 -10.916  0.00  0.00      6
ATOM   2595  O   CYS  334       8.888  59.635 -10.198  0.00  0.00      8
ATOM   2596  CB  CYS  334      10.815  57.047  -9.897  0.00  0.00      6
ATOM   2597  SG  CYS  334      12.242  56.207  -9.148  0.00  0.00     16
ATOM   2598  N   ASN  335       9.486  58.803 -12.204  0.00  0.00      7
```

FIG.23.50

```
ATOM   2599  CA  ASN   335      8.235  59.224  -12.824  0.00  0.00      6
ATOM   2600  CB  ASN   335      8.492  60.030  -14.089  0.00  0.00      6
ATOM   2601  CG  ASN   335      7.263  60.696  -14.577  0.00  0.00      6
ATOM   2602  OD1 ASN   335      6.359  60.059  -15.081  0.00  0.00      8
ATOM   2603  ND2 ASN   335      7.178  61.978  -14.345  0.00  0.00      7
ATOM   2604  C   ASN   335      7.397  57.993  -13.146  0.00  0.00      6
ATOM   2605  O   ASN   335      7.763  57.217  -14.032  0.00  0.00      8
ATOM   2606  N   PHE   336      6.307  57.804  -12.394  0.00  0.00      7
ATOM   2607  CA  PHE   336      5.405  56.674  -12.567  0.00  0.00      6
ATOM   2608  CB  PHE   336      4.208  56.808  -11.619  0.00  0.00      6
ATOM   2609  CG  PHE   336      3.161  55.748  -11.809  0.00  0.00      6
ATOM   2610  CD1 PHE   336      3.345  54.470  -11.308  0.00  0.00      6
ATOM   2611  CD2 PHE   336      2.011  56.015  -12.539  0.00  0.00      6
ATOM   2612  CE1 PHE   336      2.397  53.474  -11.544  0.00  0.00      6
ATOM   2613  CE2 PHE   336      1.067  55.029  -12.777  0.00  0.00      6
ATOM   2614  CZ  PHE   336      1.260  53.763  -12.281  0.00  0.00      6
ATOM   2615  C   PHE   336      4.928  56.535  -14.011  0.00  0.00      6
ATOM   2616  O   PHE   336      5.014  55.454  -14.590  0.00  0.00      8
ATOM   2617  N   LEU   337      4.433  57.630  -14.585  0.00  0.00      7
ATOM   2618  CA  LEU   337      3.948  57.636  -15.966  0.00  0.00      6
ATOM   2619  CB  LEU   337      3.300  58.989  -16.304  0.00  0.00      6
ATOM   2620  CG  LEU   337      1.946  59.230  -15.616  0.00  0.00      6
ATOM   2621  CD1 LEU   337      1.284  60.481  -16.148  0.00  0.00      6
```

FIG.23.51

```
ATOM   2622  CD2 LEU   337      1.015  58.057 -15.853  0.00  0.00      6
ATOM   2623  C   LEU   337      5.036  57.253 -16.989  0.00  0.00      6
ATOM   2624  O   LEU   337      4.754  56.576 -17.951  0.00  0.00      8
ATOM   2625  N   VAL   338      6.270  57.679 -16.780  0.00  0.00      7
ATOM   2626  CA  VAL   338      7.348  57.311 -17.693  0.00  0.00      6
ATOM   2627  CB  VAL   338      8.639  58.100 -17.378  0.00  0.00      6
ATOM   2628  CG1 VAL   338      9.872  57.392 -17.931  0.00  0.00      6
ATOM   2629  CG2 VAL   338      8.537  59.510 -17.943  0.00  0.00      6
ATOM   2630  C   VAL   338      7.628  55.793 -17.618  0.00  0.00      6
ATOM   2631  O   VAL   338      7.734  55.110 -18.645  0.00  0.00      8
ATOM   2632  N   ASN   339      7.756  55.272 -16.395  0.00  0.00      7
ATOM   2633  CA  ASN   339      8.008  53.847 -16.185  0.00  0.00      6
ATOM   2634  CB  ASN   339      8.241  53.573 -14.697  0.00  0.00      6
ATOM   2635  CG  ASN   339      8.321  52.086 -14.373  0.00  0.00      6
ATOM   2636  OD1 ASN   339      7.302  51.421 -14.241  0.00  0.00      8
ATOM   2637  ND2 ASN   339      9.517  51.581 -14.206  0.00  0.00      7
ATOM   2638  C   ASN   339      6.815  53.041 -16.721  0.00  0.00      6
ATOM   2639  O   ASN   339      6.996  51.990 -17.343  0.00  0.00      8
ATOM   2640  N   LEU   340      5.608  53.559 -16.514  0.00  0.00      7
ATOM   2641  CA  LEU   340      4.380  52.922 -16.983  0.00  0.00      6
ATOM   2642  CB  LEU   340      3.163  53.742 -16.516  0.00  0.00      6
ATOM   2643  CG  LEU   340      1.738  53.386 -16.972  0.00  0.00      6
ATOM   2644  CD1 LEU   340      1.170  52.220 -16.186  0.00  0.00      6
```

FIG.23.52

ATOM	2645	CD2	LEU	340	0.859	54.570	-16.748	0.00	0.00	6
ATOM	2646	C	LEU	340	4.264	52.726	-18.514	0.00	0.00	6
ATOM	2647	O	LEU	340	3.728	51.712	-18.984	0.00	0.00	8
ATOM	2648	N	GLN	341	4.729	53.714	-19.281	0.00	0.00	7
ATOM	2649	CA	GLN	341	4.616	53.709	-20.741	0.00	0.00	6
ATOM	2650	CB	GLN	341	4.306	55.106	-21.232	0.00	0.00	6
ATOM	2651	CG	GLN	341	3.049	55.688	-20.671	0.00	0.00	6
ATOM	2652	CD	GLN	341	2.919	57.129	-21.056	0.00	0.00	6
ATOM	2653	OE1	GLN	341	3.636	57.980	-20.536	0.00	0.00	8
ATOM	2654	NE2	GLN	341	2.064	57.412	-22.036	0.00	0.00	7
ATOM	2655	C	GLN	341	5.868	53.271	-21.407	0.00	0.00	6
ATOM	2656	O	GLN	341	5.967	53.290	-22.637	0.00	0.00	8
ATOM	2657	N	TYR	342	6.840	52.918	-20.586	0.00	0.00	7
ATOM	2658	CA	TYR	342	8.132	52.492	-21.068	0.00	0.00	6
ATOM	2659	CB	TYR	342	9.163	52.533	-19.929	0.00	0.00	6
ATOM	2660	CG	TYR	342	10.586	52.464	-20.404	0.00	0.00	6
ATOM	2661	CD1	TYR	342	11.278	53.628	-20.702	0.00	0.00	6
ATOM	2662	CE1	TYR	342	12.557	53.586	-21.194	0.00	0.00	6
ATOM	2663	CD2	TYR	342	11.215	51.249	-20.619	0.00	0.00	6
ATOM	2664	CE2	TYR	342	12.500	51.200	-21.121	0.00	0.00	6
ATOM	2665	CZ	TYR	342	13.156	52.378	-21.413	0.00	0.00	6
ATOM	2666	OH	TYR	342	14.423	52.395	-21.943	0.00	0.00	8
ATOM	2667	C	TYR	342	8.085	51.099	-21.687	0.00	0.00	6

FIG.23.53

```
ATOM   2668  O   TYR   342      7.511  50.170  -21.113  0.00  0.00      8
ATOM   2669  N   ARG   343      8.705  50.985  -22.867  0.00  0.00      7
ATOM   2670  CA  ARG   343      8.786  49.742  -23.612  0.00  0.00      6
ATOM   2671  CB  ARG   343      8.255  49.912  -25.031  0.00  0.00      6
ATOM   2672  CG  ARG   343      6.815  50.370  -25.083  0.00  0.00      6
ATOM   2673  CD  ARG   343      5.858  49.437  -24.311  0.00  0.00      6
ATOM   2674  NE  ARG   343      4.527  50.043  -24.164  0.00  0.00      7
ATOM   2675  CZ  ARG   343      3.917  50.284  -23.003  0.00  0.00      6
ATOM   2676  NH1 ARG   343      4.483  49.951  -21.842  0.00  0.00      7
ATOM   2677  NH2 ARG   343      2.797  50.997  -23.001  0.00  0.00      7
ATOM   2678  C   ARG   343     10.200  49.210  -23.643  0.00  0.00      6
ATOM   2679  O   ARG   343     11.126  49.841  -24.174  0.00  0.00      8
ATOM   2680  N   ARG   344     10.345  48.050  -23.017  0.00  0.00      7
ATOM   2681  CA  ARG   344     11.602  47.344  -22.925  0.00  0.00      6
ATOM   2682  CB  ARG   344     11.554  46.402  -21.714  0.00  0.00      6
ATOM   2683  CG  ARG   344     11.203  47.131  -20.404  0.00  0.00      6
ATOM   2684  CD  ARG   344     11.156  46.157  -19.244  0.00  0.00      6
ATOM   2685  NE  ARG   344     11.224  46.784  -17.926  0.00  0.00      7
ATOM   2686  CZ  ARG   344     10.283  47.585  -17.455  0.00  0.00      6
ATOM   2687  NH1 ARG   344      9.233  47.849  -18.207  0.00  0.00      7
ATOM   2688  NH2 ARG   344     10.354  48.075  -16.221  0.00  0.00      7
ATOM   2689  C   ARG   344     11.731  46.579  -24.253  0.00  0.00      6
ATOM   2690  O   ARG   344     10.823  45.871  -24.657  0.00  0.00      8
```

FIG.23.54

```
ATOM   2691  N   LEU   345      12.834  46.779 -24.953  0.00  0.00      7
ATOM   2692  CA  LEU   345      13.022  46.146 -26.238  0.00  0.00      6
ATOM   2693  CB  LEU   345      13.413  47.193 -27.302  0.00  0.00      6
ATOM   2694  CG  LEU   345      12.566  48.468 -27.368  0.00  0.00      6
ATOM   2695  CD1 LEU   345      13.194  49.422 -28.350  0.00  0.00      6
ATOM   2696  CD2 LEU   345      11.127  48.192 -27.708  0.00  0.00      6
ATOM   2697  C   LEU   345      14.059  45.064 -26.148  0.00  0.00      6
ATOM   2698  O   LEU   345      13.855  44.001 -26.687  0.00  0.00      8
ATOM   2699  N   TYR   346      15.176  45.312 -25.475  0.00  0.00      7
ATOM   2700  CA  TYR   346      16.195  44.279 -25.365  0.00  0.00      6
ATOM   2701  CB  TYR   346      17.563  44.886 -25.225  0.00  0.00      6
ATOM   2702  CG  TYR   346      17.875  45.813 -26.336  0.00  0.00      6
ATOM   2703  CD1 TYR   346      17.509  47.151 -26.265  0.00  0.00      6
ATOM   2704  CE1 TYR   346      17.801  48.024 -27.293  0.00  0.00      6
ATOM   2705  CD2 TYR   346      18.541  45.364 -27.464  0.00  0.00      6
ATOM   2706  CE2 TYR   346      18.842  46.230 -28.498  0.00  0.00      6
ATOM   2707  CZ  TYR   346      18.472  47.564 -28.406  0.00  0.00      6
ATOM   2708  OH  TYR   346      18.816  48.451 -29.395  0.00  0.00      8
ATOM   2709  C   TYR   346      15.966  43.379 -24.176  0.00  0.00      6
ATOM   2710  O   TYR   346      15.682  43.851 -23.072  0.00  0.00      8
ATOM   2711  N   ARG   347      16.170  42.088 -24.394  0.00  0.00      7
ATOM   2712  CA  ARG   347      15.997  41.087 -23.349  0.00  0.00      6
ATOM   2713  CB  ARG   347      15.299  39.857 -23.930  0.00  0.00      6
```

FIG.23.55

ATOM	2714	CG	ARG	347	13.824	40.092	-24.184	0.00	0.00	6
ATOM	2715	CD	ARG	347	13.029	39.837	-22.915	0.00	0.00	6
ATOM	2716	NE	ARG	347	12.346	41.018	-22.405	0.00	0.00	7
ATOM	2717	CZ	ARG	347	11.690	41.040	-21.250	0.00	0.00	6
ATOM	2718	NH1	ARG	347	11.636	39.942	-20.489	0.00	0.00	7
ATOM	2719	NH2	ARG	347	11.064	42.150	-20.872	0.00	0.00	7
ATOM	2720	C	ARG	347	17.355	40.705	-22.758	0.00	0.00	6
ATOM	2721	O	ARG	347	17.438	40.211	-21.637	0.00	0.00	8
ATOM	2722	N	SER	348	18.411	40.980	-23.510	0.00	0.00	7
ATOM	2723	CA	SER	348	19.768	40.667	-23.094	0.00	0.00	6
ATOM	2724	CB	SER	348	20.129	39.264	-23.611	0.00	0.00	6
ATOM	2725	OG	SER	348	21.509	39.005	-23.442	0.00	0.00	8
ATOM	2726	C	SER	348	20.727	41.700	-23.704	0.00	0.00	6
ATOM	2727	O	SER	348	20.426	42.262	-24.754	0.00	0.00	8
ATOM	2728	N	MET	349	21.876	41.916	-23.052	0.00	0.00	7
ATOM	2729	CA	MET	349	22.910	42.839	-23.522	0.00	0.00	6
ATOM	2730	CB	MET	349	23.375	43.751	-22.380	0.00	0.00	6
ATOM	2731	CG	MET	349	22.376	44.853	-21.983	0.00	0.00	6
ATOM	2732	SD	MET	349	22.063	46.109	-23.244	0.00	0.00	16
ATOM	2733	CE	MET	349	20.524	45.599	-23.844	0.00	0.00	6
ATOM	2734	C	MET	349	24.130	42.128	-24.122	0.00	0.00	6
ATOM	2735	O	MET	349	25.182	42.732	-24.298	0.00	0.00	8
ATOM	2736	N	ASN	350	23.974	40.854	-24.469	0.00	0.00	7

FIG.23.56

ATOM	2737	CA	ASN	350	25.068	40.066	-25.026	0.00	0.00	6
ATOM	2738	CB	ASN	350	24.620	38.629	-25.302	0.00	0.00	6
ATOM	2739	CG	ASN	350	24.814	37.700	-24.102	0.00	0.00	6
ATOM	2740	OD1	ASN	350	25.925	37.213	-23.845	0.00	0.00	8
ATOM	2741	ND2	ASN	350	23.724	37.422	-23.379	0.00	0.00	7
ATOM	2742	C	ASN	350	25.652	40.659	-26.293	0.00	0.00	6
ATOM	2743	O	ASN	350	26.880	40.737	-26.410	0.00	0.00	8
ATOM	2871	N	LEU	366	31.679	45.222	-14.828	0.00	0.00	7
ATOM	2872	CA	LEU	366	30.314	45.021	-14.325	0.00	0.00	6
ATOM	2873	CB	LEU	366	29.564	43.843	-14.987	0.00	0.00	6
ATOM	2874	CG	LEU	366	28.817	44.056	-16.331	0.00	0.00	6
ATOM	2875	CD1	LEU	366	29.791	44.164	-17.487	0.00	0.00	6
ATOM	2876	CD2	LEU	366	27.880	42.910	-16.607	0.00	0.00	6
ATOM	2877	C	LEU	366	30.610	44.731	-12.845	0.00	0.00	6
ATOM	2878	O	LEU	366	31.409	43.857	-12.529	0.00	0.00	8
ATOM	2879	N	TYR	367	30.026	45.511	-11.940	0.00	0.00	7
ATOM	2880	CA	TYR	367	30.273	45.313	-10.505	0.00	0.00	6
ATOM	2881	CB	TYR	367	31.151	46.462	-9.960	0.00	0.00	6
ATOM	2882	CG	TYR	367	30.489	47.835	-10.015	0.00	0.00	6
ATOM	2883	CD1	TYR	367	29.581	48.221	-9.031	0.00	0.00	6
ATOM	2884	CE1	TYR	367	28.979	49.457	-9.065	0.00	0.00	6
ATOM	2885	CD2	TYR	367	30.775	48.746	-11.052	0.00	0.00	6

FIG.23.57

```
ATOM   2886  CE2 TYR   367      30.155  50.021 -11.103  0.00  0.00      6
ATOM   2887  CZ  TYR   367      29.257  50.370 -10.102  0.00  0.00      6
ATOM   2888  OH  TYR   367      28.634  51.610 -10.097  0.00  0.00      8
ATOM   2889  C   TYR   367      28.946  45.193  -9.755  0.00  0.00      6
ATOM   2890  O   TYR   367      28.015  45.963 -10.020  0.00  0.00      8
ATOM   2891  N   ASN   368      28.813  44.161  -8.920  0.00  0.00      7
ATOM   2892  CA  ASN   368      27.582  43.978  -8.159  0.00  0.00      6
ATOM   2893  CB  ASN   368      26.822  42.715  -8.584  0.00  0.00      6
ATOM   2894  CG  ASN   368      26.280  42.805  -9.977  0.00  0.00      6
ATOM   2895  OD1 ASN   368      27.037  42.925 -10.919  0.00  0.00      8
ATOM   2896  ND2 ASN   368      24.976  42.657 -10.126  0.00  0.00      7
ATOM   2897  C   ASN   368      27.766  43.869  -6.640  0.00  0.00      6
ATOM   2898  O   ASN   368      28.737  43.286  -6.154  0.00  0.00      8
ATOM   2899  N   GLY   369      26.819  44.429  -5.900  0.00  0.00      7
ATOM   2900  CA  GLY   369      26.840  44.297  -4.463  0.00  0.00      6
ATOM   2901  C   GLY   369      26.143  42.956  -4.271  0.00  0.00      6
ATOM   2902  O   GLY   369      25.030  42.750  -4.816  0.00  0.00      8
ATOM   2903  N   ASP   370      26.777  42.072  -3.497  0.00  0.00      7
ATOM   2904  CA  ASP   370      26.279  40.724  -3.247  0.00  0.00      6
ATOM   2905  CB  ASP   370      27.431  39.815  -2.852  0.00  0.00      6
ATOM   2906  CG  ASP   370      28.041  40.174  -1.506  0.00  0.00      6
ATOM   2907  OD1 ASP   370      27.461  40.971  -0.722  0.00  0.00      8
ATOM   2908  OD2 ASP   370      29.117  39.629  -1.242  0.00  0.00      8
```

FIG.23.58

```
ATOM   2909  C   ASP  370      25.083  40.467  -2.331  0.00  0.00      6
ATOM   2910  O   ASP  370      24.723  39.314  -2.105  0.00  0.00      8
ATOM   2911  N   VAL  371      24.463  41.509  -1.787  0.00  0.00      7
ATOM   2912  CA  VAL  371      23.286  41.296  -0.946  0.00  0.00      6
ATOM   2913  CB  VAL  371      23.473  41.749   0.535  0.00  0.00      6
ATOM   2914  CG1 VAL  371      24.644  41.016   1.129  0.00  0.00      6
ATOM   2915  CG2 VAL  371      23.657  43.245   0.652  0.00  0.00      6
ATOM   2916  C   VAL  371      22.070  41.919  -1.575  0.00  0.00      6
ATOM   2917  O   VAL  371      21.030  42.015  -0.948  0.00  0.00      8
ATOM   2918  N   ASP  372      22.217  42.318  -2.840  0.00  0.00      7
ATOM   2919  CA  ASP  372      21.128  42.895  -3.626  0.00  0.00      6
ATOM   2920  CB  ASP  372      21.699  43.804  -4.726  0.00  0.00      6
ATOM   2921  CG  ASP  372      20.643  44.258  -5.734  0.00  0.00      6
ATOM   2922  OD1 ASP  372      19.493  44.548  -5.349  0.00  0.00      8
ATOM   2923  OD2 ASP  372      20.983  44.338  -6.927  0.00  0.00      8
ATOM   2924  C   ASP  372      20.328  41.763  -4.266  0.00  0.00      6
ATOM   2925  O   ASP  372      20.893  40.758  -4.709  0.00  0.00      8
ATOM   2926  N   MET  373      19.014  41.907  -4.277  0.00  0.00      7
ATOM   2927  CA  MET  373      18.170  40.910  -4.895  0.00  0.00      6
ATOM   2928  CB  MET  373      17.145  40.386  -3.902  0.00  0.00      6
ATOM   2929  CG  MET  373      17.727  39.704  -2.663  0.00  0.00      6
ATOM   2930  SD  MET  373      16.347  38.918  -1.784  0.00  0.00     16
ATOM   2931  CE  MET  373      15.432  40.310  -1.195  0.00  0.00      6
```

FIG:23.59

ATOM	2932	C	MET	373	17.449	41.461	-6.159	0.00	0.00	6
ATOM	2933	O	MET	373	16.714	40.713	-6.808	0.00	0.00	8
ATOM	2934	N	ALA	374	17.604	42.756	-6.486	0.00	0.00	7
ATOM	2935	CA	ALA	374	16.966	43.319	-7.707	0.00	0.00	6
ATOM	2936	CB	ALA	374	16.817	44.826	-7.626	0.00	0.00	6
ATOM	2937	C	ALA	374	17.781	42.911	-8.945	0.00	0.00	6
ATOM	2938	O	ALA	374	17.216	42.464	-9.931	0.00	0.00	8
ATOM	2939	N	CYS	375	19.107	43.021	-8.857	0.00	0.00	7
ATOM	2940	CA	CYS	375	20.036	42.591	-9.923	0.00	0.00	6
ATOM	2941	CB	CYS	375	20.530	43.745	-10.836	0.00	0.00	6
ATOM	2942	SG	CYS	375	19.227	44.512	-11.816	0.00	0.00	16
ATOM	2943	C	CYS	375	21.200	41.889	-9.228	0.00	0.00	6
ATOM	2944	O	CYS	375	22.352	42.340	-9.274	0.00	0.00	8
ATOM	2945	N	ASN	376	20.882	40.754	-8.596	0.00	0.00	7
ATOM	2946	CA	ASN	376	21.859	39.979	-7.842	0.00	0.00	6
ATOM	2947	CB	ASN	376	21.235	38.679	-7.301	0.00	0.00	6
ATOM	2948	CG	ASN	376	21.160	37.559	-8.342	0.00	0.00	6
ATOM	2949	OD1	ASN	376	22.146	36.856	-8.611	0.00	0.00	8
ATOM	2950	ND2	ASN	376	19.981	37.380	-8.909	0.00	0.00	7
ATOM	2951	C	ASN	376	23.172	39.743	-8.579	0.00	0.00	6
ATOM	2952	O	ASN	376	23.210	39.739	-9.808	0.00	0.00	8
ATOM	2953	N	PHE	377	24.257	39.611	-7.815	0.00	0.00	7
ATOM	2954	CA	PHE	377	25.581	39.414	-8.368	0.00	0.00	6

FIG.23.60

```
ATOM   2955  CB  PHE   377      26.608  39.345  -7.230  0.00  0.00      6
ATOM   2956  CG  PHE   377      26.650  38.006  -6.544  0.00  0.00      6
ATOM   2957  CD1 PHE   377      27.546  37.009  -6.973  0.00  0.00      6
ATOM   2958  CD2 PHE   377      25.732  37.687  -5.541  0.00  0.00      6
ATOM   2959  CE1 PHE   377      27.505  35.737  -6.409  0.00  0.00      6
ATOM   2960  CE2 PHE   377      25.702  36.407  -4.982  0.00  0.00      6
ATOM   2961  CZ  PHE   377      26.582  35.447  -5.417  0.00  0.00      6
ATOM   2962  C   PHE   377      25.725  38.162  -9.248  0.00  0.00      6
ATOM   2963  O   PHE   377      26.504  38.155 -10.193  0.00  0.00      8
ATOM   2964  N   MET   378      25.019  37.088  -8.909  0.00  0.00      7
ATOM   2965  CA  MET   378      25.152  35.850  -9.667  0.00  0.00      6
ATOM   2966  CB  MET   378      24.545  34.650  -8.905  0.00  0.00      6
ATOM   2967  CG  MET   378      24.953  33.295  -9.501  0.00  0.00      6
ATOM   2968  SD  MET   378      24.600  31.846  -8.493  0.00  0.00     16
ATOM   2969  CE  MET   378      26.143  31.824  -7.695  0.00  0.00      6
ATOM   2970  C   MET   378      24.610  35.957 -11.098  0.00  0.00      6
ATOM   2971  O   MET   378      25.225  35.441 -12.023  0.00  0.00      8
ATOM   2972  N   GLY   379      23.483  36.639 -11.273  0.00  0.00      7
ATOM   2973  CA  GLY   379      22.916  36.827 -12.600  0.00  0.00      6
ATOM   2974  C   GLY   379      23.909  37.491 -13.542  0.00  0.00      6
ATOM   2975  O   GLY   379      24.087  37.054 -14.695  0.00  0.00      8
ATOM   2976  N   ASP   380      24.594  38.516 -13.027  0.00  0.00      7
ATOM   2977  CA  ASP   380      25.599  39.244 -13.790  0.00  0.00      6
```

FIG.23.61

```
ATOM   2978  CB  ASP   380      25.805  40.681  -13.267   0.00   0.00      6
ATOM   2979  CG  ASP   380      24.776  41.666  -13.830   0.00   0.00      6
ATOM   2980  OD1 ASP   380      24.528  41.606  -15.046   0.00   0.00      8
ATOM   2981  OD2 ASP   380      24.210  42.487  -13.059   0.00   0.00      8
ATOM   2982  C   ASP   380      26.920  38.522  -13.897   0.00   0.00      6
ATOM   2983  O   ASP   380      27.678  38.785  -14.828   0.00   0.00      8
ATOM   2984  N   GLU   381      27.240  37.652  -12.942   0.00   0.00      7
ATOM   2985  CA  GLU   381      28.486  36.891  -13.051   0.00   0.00      6
ATOM   2986  CB  GLU   381      28.885  36.216  -11.729   0.00   0.00      6
ATOM   2987  CG  GLU   381      30.186  35.454  -11.899   0.00   0.00      6
ATOM   2988  CD  GLU   381      30.971  35.235  -10.614   0.00   0.00      6
ATOM   2989  OE1 GLU   381      30.421  35.405   -9.499   0.00   0.00      8
ATOM   2990  OE2 GLU   381      32.172  34.904  -10.729   0.00   0.00      8
ATOM   2991  C   GLU   381      28.276  35.846  -14.151   0.00   0.00      6
ATOM   2992  O   GLU   381      29.142  35.598  -14.985   0.00   0.00      8
=============================================================================
ATOM   3337  N   THR   423      32.461  41.846   -7.442   0.00   0.00      7
ATOM   3338  CA  THR   423      31.418  41.928   -6.429   0.00   0.00      6
ATOM   3339  CB  THR   423      31.025  40.509   -5.813   0.00   0.00      6
ATOM   3340  OG1 THR   423      32.118  39.973   -5.041   0.00   0.00      8
ATOM   3341  CG2 THR   423      30.632  39.507   -6.916   0.00   0.00      6
ATOM   3342  C   THR   423      31.897  42.867   -5.308   0.00   0.00      6
ATOM   3343  O   THR   423      33.109  43.081   -5.129   0.00   0.00      8
```

FIG.23.62

ATOM	3344	N	ILE	424	30.947	43.461	-4.601	0.00	0.00	7
ATOM	3345	CA	ILE	424	31.261	44.318	-3.471	0.00	0.00	6
ATOM	3346	CB	ILE	424	30.743	45.798	-3.651	0.00	0.00	6
ATOM	3347	CG2	ILE	424	30.957	46.572	-2.378	0.00	0.00	6
ATOM	3348	CG1	ILE	424	31.541	46.519	-4.732	0.00	0.00	6
ATOM	3349	CD1	ILE	424	31.051	46.297	-6.131	0.00	0.00	6
ATOM	3350	C	ILE	424	30.564	43.580	-2.297	0.00	0.00	6
ATOM	3351	O	ILE	424	29.328	43.502	-2.233	0.00	0.00	8
ATOM	3352	N	LYS	425	31.369	42.972	-1.429	0.00	0.00	7
ATOM	3353	CA	LYS	425	30.836	42.210	-0.304	0.00	0.00	6
ATOM	3354	CB	LYS	425	31.948	41.450	0.418	0.00	0.00	6
ATOM	3355	CG	LYS	425	31.432	40.315	1.321	0.00	0.00	6
ATOM	3356	CD	LYS	425	32.576	39.443	1.761	0.00	0.00	6
ATOM	3357	CE	LYS	425	33.645	40.231	2.555	0.00	0.00	6
ATOM	3358	NZ	LYS	425	33.124	40.787	3.851	0.00	0.00	7
ATOM	3359	C	LYS	425	30.030	43.030	0.689	0.00	0.00	6
ATOM	3360	O	LYS	425	30.527	43.973	1.265	0.00	0.00	8
ATOM	3361	N	GLY	426	28.802	42.605	0.930	0.00	0.00	7
ATOM	3362	CA	GLY	426	27.949	43.318	1.845	0.00	0.00	6
ATOM	3363	C	GLY	426	27.225	44.514	1.269	0.00	0.00	6
ATOM	3364	O	GLY	426	26.438	45.129	1.979	0.00	0.00	8
ATOM	3365	N	ALA	427	27.488	44.887	0.024	0.00	0.00	7
ATOM	3366	CA	ALA	427	26.777	46.026	-0.547	0.00	0.00	6

FIG.23.63

```
ATOM   3367  CB  ALA   427      27.676  46.782  -1.497  0.00  0.00      6
ATOM   3368  C   ALA   427      25.509  45.546  -1.257  0.00  0.00      6
ATOM   3369  O   ALA   427      25.397  44.378  -1.634  0.00  0.00      8
ATOM   3370  N   GLY   428      24.531  46.420  -1.386  0.00  0.00      7
ATOM   3371  CA  GLY   428      23.308  46.065  -2.067  0.00  0.00      6
ATOM   3372  C   GLY   428      23.251  46.665  -3.475  0.00  0.00      6
ATOM   3373  O   GLY   428      24.271  46.940  -4.081  0.00  0.00      8
ATOM   3374  N   HIS   429      22.050  46.931  -3.963  0.00  0.00      7
ATOM   3375  CA  HIS   429      21.827  47.501  -5.287  0.00  0.00      6
ATOM   3376  CB  HIS   429      20.349  47.795  -5.452  0.00  0.00      6
ATOM   3377  CG  HIS   429      19.902  47.920  -6.868  0.00  0.00      6
ATOM   3378  CD2 HIS   429      19.239  48.909  -7.512  0.00  0.00      6
ATOM   3379  ND1 HIS   429      20.044  46.897  -7.779  0.00  0.00      7
ATOM   3380  CE1 HIS   429      19.471  47.241  -8.919  0.00  0.00      6
ATOM   3381  NE2 HIS   429      18.978  48.456  -8.787  0.00  0.00      7
ATOM   3382  C   HIS   429      22.593  48.776  -5.541  0.00  0.00      6
ATOM   3383  O   HIS   429      23.153  48.973  -6.629  0.00  0.00      8
ATOM   3384  N   MET   430      22.569  49.670  -4.559  0.00  0.00      7
ATOM   3385  CA  MET   430      23.236  50.957  -4.665  0.00  0.00      6
ATOM   3386  CB  MET   430      22.297  52.036  -4.162  0.00  0.00      6
ATOM   3387  CG  MET   430      21.019  52.050  -4.968  0.00  0.00      6
ATOM   3388  SD  MET   430      19.807  53.164  -4.342  0.00  0.00     16
ATOM   3389  CE  MET   430      20.554  54.745  -4.772  0.00  0.00      6
```

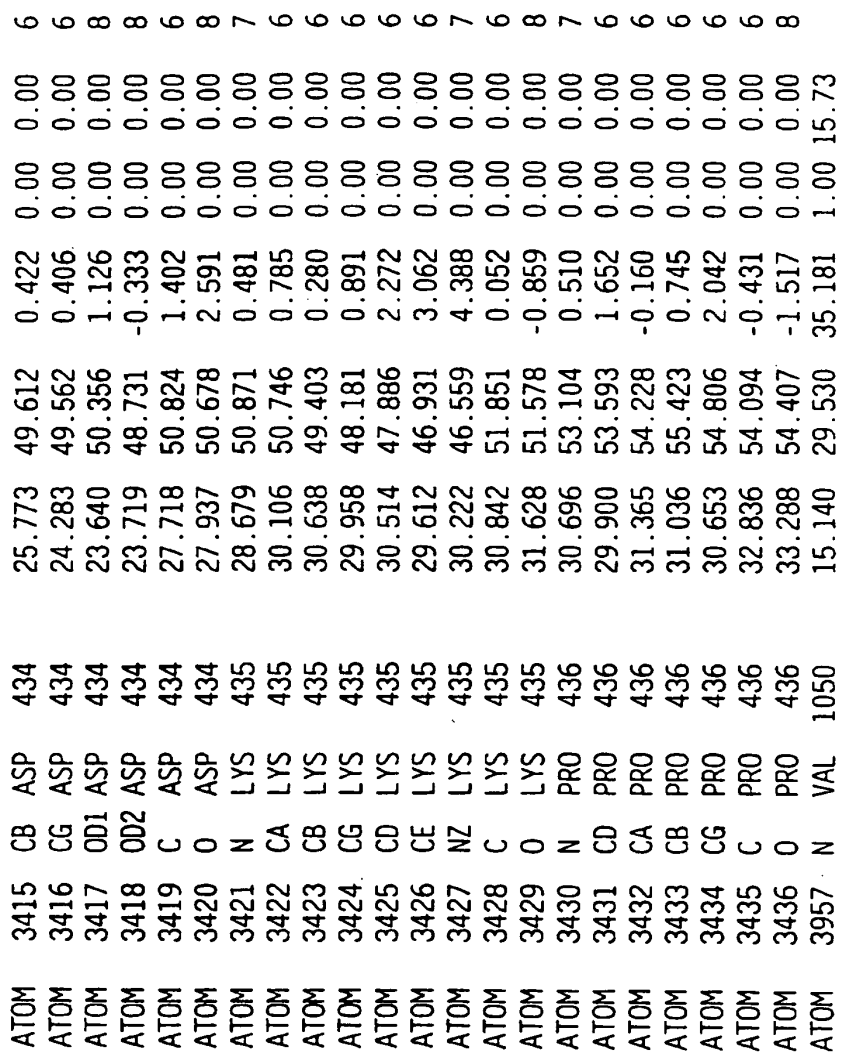
FIG.23.64

```
ATOM   3390  C   MET  430      24.528  50.927  -3.916  0.00  0.00      6
ATOM   3391  O   MET  430      24.689  51.502  -2.823  0.00  0.00      8
ATOM   3392  N   VAL  431      25.478  50.271  -4.565  0.00  0.00      7
ATOM   3393  CA  VAL  431      26.806  50.048  -4.060  0.00  0.00      6
ATOM   3394  CB  VAL  431      27.684  49.360  -5.167  0.00  0.00      6
ATOM   3395  CG1 VAL  431      29.177  49.533  -4.896  0.00  0.00      6
ATOM   3396  CG2 VAL  431      27.338  47.848  -5.244  0.00  0.00      6
ATOM   3397  C   VAL  431      27.542  51.212  -3.372  0.00  0.00      6
ATOM   3398  O   VAL  431      28.055  51.016  -2.257  0.00  0.00      8
ATOM   3399  N   PRO  432      27.567  52.436  -3.980  0.00  0.00      7
ATOM   3400  CD  PRO  432      27.044  52.899  -5.272  0.00  0.00      6
ATOM   3401  CA  PRO  432      28.279  53.543  -3.332  0.00  0.00      6
ATOM   3402  CB  PRO  432      28.249  54.636  -4.395  0.00  0.00      6
ATOM   3403  CG  PRO  432      28.062  53.906  -5.653  0.00  0.00      6
ATOM   3404  C   PRO  432      27.591  53.999  -2.053  0.00  0.00      6
ATOM   3405  O   PRO  432      28.227  54.508  -1.152  0.00  0.00      8
ATOM   3406  N   THR  433      26.281  53.897  -2.012  0.00  0.00      7
ATOM   3407  CA  THR  433      25.570  54.271  -0.824  0.00  0.00      6
ATOM   3408  CB  THR  433      24.089  54.155  -1.039  0.00  0.00      6
ATOM   3409  OG1 THR  433      23.714  54.976  -2.139  0.00  0.00      8
ATOM   3410  CG2 THR  433      23.341  54.593   0.198  0.00  0.00      6
ATOM   3411  C   THR  433      25.969  53.286   0.288  0.00  0.00      6
ATOM   3412  O   THR  433      26.312  53.701   1.402  0.00  0.00      8
```

FIG.23.65

```
ATOM   3413  N   ASP  434      25.969  51.990  -0.040  0.00  0.00   7
ATOM   3414  CA  ASP  434      26.285  50.953   0.918  0.00  0.00   6
ATOM   3415  CB  ASP  434      25.773  49.612   0.422  0.00  0.00   6
ATOM   3416  CG  ASP  434      24.283  49.562   0.406  0.00  0.00   6
ATOM   3417  OD1 ASP  434      23.640  50.356   1.126  0.00  0.00   8
ATOM   3418  OD2 ASP  434      23.719  48.731  -0.333  0.00  0.00   8
ATOM   3419  C   ASP  434      27.718  50.824   1.402  0.00  0.00   6
ATOM   3420  O   ASP  434      27.937  50.678   2.591  0.00  0.00   8
ATOM   3421  N   LYS  435      28.679  50.871   0.481  0.00  0.00   7
ATOM   3422  CA  LYS  435      30.106  50.746   0.785  0.00  0.00   6
ATOM   3423  CB  LYS  435      30.638  49.403   0.280  0.00  0.00   6
ATOM   3424  CG  LYS  435      29.958  48.181  53.906 -5.653  0.00  0.00   6
ATOM   3404  C   PRO  432      27.591  53.999  -2.053  0.00  0.00   6
ATOM   3405  O   PRO  432      28.227  54.508  -1.152  0.00  0.00   8
ATOM   3406  N   THR  433      26.281  53.897  -2.012  0.00  0.00   7
ATOM   3407  CA  THR  433      25.570  54.271  -0.824  0.00  0.00   6
ATOM   3408  CB  THR  433      24.089  54.155  -1.039  0.00  0.00   6
ATOM   3409  OG1 THR  433      23.714  54.976  -2.139  0.00  0.00   8
ATOM   3410  CG2 THR  433      23.341  54.593   0.198  0.00  0.00   6
ATOM   3411  C   THR  433      25.969  53.286   0.288  0.00  0.00   6
ATOM   3412  O   THR  433      26.312  53.701   1.402  0.00  0.00   8
ATOM   3413  N   ASP  434      25.969  51.990  -0.040  0.00  0.00   7
ATOM   3414  CA  ASP  434      26.285  50.953   0.918  0.00  0.00   6
```

FIG.23.66



```
ATOM   3415  CB  ASP   434      25.773  49.612   0.422  0.00  0.00      6
ATOM   3416  CG  ASP   434      24.283  49.562   0.406  0.00  0.00      6
ATOM   3417  OD1 ASP   434      23.640  50.356   1.126  0.00  0.00      8
ATOM   3418  OD2 ASP   434      23.719  48.731  -0.333  0.00  0.00      8
ATOM   3419  C   ASP   434      27.718  50.824   1.402  0.00  0.00      6
ATOM   3420  O   ASP   434      27.937  50.678   2.591  0.00  0.00      8
ATOM   3421  N   LYS   435      28.679  50.871   0.481  0.00  0.00      7
ATOM   3422  CA  LYS   435      30.106  50.746   0.785  0.00  0.00      6
ATOM   3423  CB  LYS   435      30.638  49.403   0.280  0.00  0.00      6
ATOM   3424  CG  LYS   435      29.958  48.181   0.891  0.00  0.00      6
ATOM   3425  CD  LYS   435      30.514  47.886   2.272  0.00  0.00      6
ATOM   3426  CE  LYS   435      29.612  46.931   3.062  0.00  0.00      6
ATOM   3427  NZ  LYS   435      30.222  46.559   4.388  0.00  0.00      7
ATOM   3428  C   LYS   435      30.842  51.851   0.052  0.00  0.00      6
ATOM   3429  O   LYS   435      31.628  51.578  -0.859  0.00  0.00      8
ATOM   3430  N   PRO   436      30.696  53.104   0.510  0.00  0.00      7
ATOM   3431  CD  PRO   436      29.900  53.593   1.652  0.00  0.00      6
ATOM   3432  CA  PRO   436      31.365  54.228  -0.160  0.00  0.00      6
ATOM   3433  CB  PRO   436      31.036  55.423   0.745  0.00  0.00      6
ATOM   3434  CG  PRO   436      30.653  54.806   2.042  0.00  0.00      6
ATOM   3435  C   PRO   436      32.836  54.094  -0.431  0.00  0.00      6
ATOM   3436  O   PRO   436      33.288  54.407  -1.517  0.00  0.00      8
ATOM   3957  N   VAL  1050      15.140  29.530  35.181  1.00 15.73
```

FIG.23.67

```
ATOM   3958  CA  VAL  1050      16.577  29.441  35.363  1.00 14.43
ATOM   3959  CB  VAL  1050      16.982  28.406  36.419  1.00 13.95
ATOM   3960  CG1 VAL  1050      18.474  28.227  36.434  1.00  8.21
ATOM   3961  CG2 VAL  1050      16.510  28.872  37.775  1.00 15.34
ATOM   3962  C   VAL  1050      17.032  29.009  33.986  1.00 14.76
ATOM   3963  O   VAL  1050      16.553  28.007  33.424  1.00 13.00
ATOM   3964  N   VAL  1051      17.897  29.816  33.404  1.00 16.60
ATOM   3965  CA  VAL  1051      18.377  29.535  32.081  1.00 12.64
ATOM   3966  CB  VAL  1051      18.036  30.694  31.142  1.00 10.77
ATOM   3967  CG1 VAL  1051      18.788  30.533  29.820  1.00 16.16
ATOM   3968  CG2 VAL  1051      16.516  30.733  30.920  1.00  6.39
ATOM   3969  C   VAL  1051      19.851  29.284  32.085  1.00  9.28
ATOM   3970  O   VAL  1051      20.626  30.139  32.502  1.00 11.50
ATOM   3971  N   LEU  1052      20.236  28.083  31.679  1.00 11.40
ATOM   3972  CA  LEU  1052      21.648  27.747  31.627  1.00 13.06
ATOM   3973  CB  LEU  1052      21.843  26.230  31.762  1.00  7.02
ATOM   3974  CG  LEU  1052      23.201  25.660  31.327  1.00 11.57
ATOM   3975  CD1 LEU  1052      24.306  26.114  32.254  1.00  9.95
ATOM   3976  CD2 LEU  1052      23.137  24.141  31.274  1.00 10.63
ATOM   3977  C   LEU  1052      22.145  28.195  30.272  1.00 13.38
ATOM   3978  O   LEU  1052      21.449  28.001  29.287  1.00 12.15
ATOM   3979  N   TRP  1053      23.310  28.826  30.218  1.00 12.99
ATOM   3980  CA  TRP  1053      23.874  29.211  28.941  1.00 10.31
```

FIG.23.68

```
ATOM   3981  CB  TRP  1053      24.008  30.728  28.773  1.00  8.17
ATOM   3982  CG  TRP  1053      24.769  31.089  27.475  1.00  4.04
ATOM   3983  CD2 TRP  1053      24.206  31.194  26.154  1.00  2.00
ATOM   3984  CE2 TRP  1053      25.251  31.538  25.278  1.00  2.00
ATOM   3985  CE3 TRP  1053      22.910  31.038  25.633  1.00  2.70
ATOM   3986  CD1 TRP  1053      26.100  31.356  27.342  1.00  2.00
ATOM   3987  NE1 TRP  1053      26.397  31.632  26.026  1.00  5.30
ATOM   3988  CZ2 TRP  1053      25.046  31.736  23.907  1.00  2.00
ATOM   3989  CZ3 TRP  1053      22.709  31.237  24.251  1.00  3.36
ATOM   3990  CH2 TRP  1053      23.775  31.581  23.418  1.00  2.00
ATOM   3991  C   TRP  1053      25.250  28.599  28.795  1.00  7.60
ATOM   3992  O   TRP  1053      26.103  28.778  29.660  1.00  9.96
ATOM   3993  N   LEU  1054      25.463  27.928  27.670  1.00  7.58
ATOM   3994  CA  LEU  1054      26.747  27.323  27.360  1.00  5.66
ATOM   3995  CB  LEU  1054      26.631  25.781  27.347  1.00  9.03
ATOM   3996  CG  LEU  1054      26.265  24.981  28.612  1.00 11.45
ATOM   3997  CD1 LEU  1054      26.086  23.509  28.252  1.00  9.35
ATOM   3998  CD2 LEU  1054      27.350  25.110  29.680  1.00 10.73
ATOM   3999  C   LEU  1054      27.265  27.796  25.993  1.00  7.91
ATOM   4000  O   LEU  1054      26.510  27.853  25.020  1.00  8.23
ATOM   4001  N   ASN  1055      28.527  28.200  25.939  1.00 11.04
ATOM   4002  CA  ASN  1055      29.157  28.594  24.684  1.00 14.62
ATOM   4003  CB  ASN  1055      30.210  29.701  24.876  1.00 10.71
```

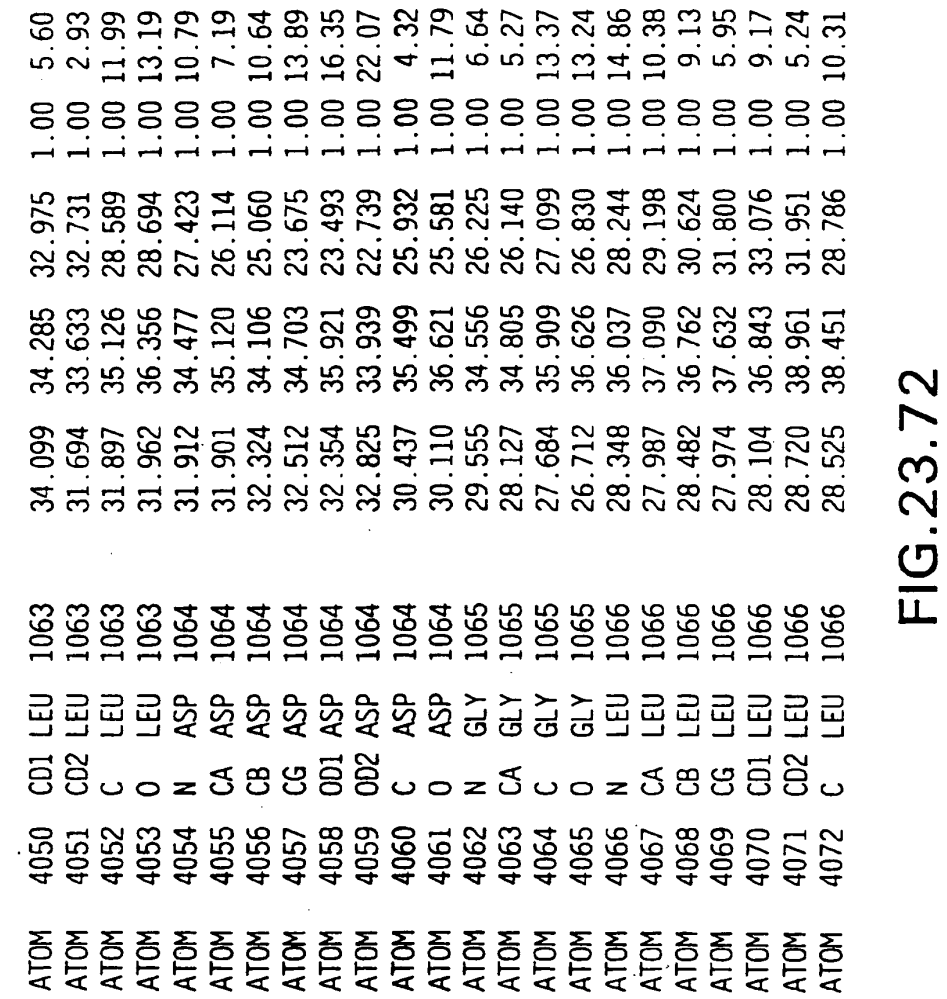
FIG.23.69

```
ATOM   4004  CG  ASN  1055      29.596  31.086  24.729  1.00 15.63
ATOM   4005  OD1 ASN  1055      29.153  31.682  25.694  1.00 10.45
ATOM   4006  ND2 ASN  1055      29.479  31.554  23.497  1.00  9.67
ATOM   4007  C   ASN  1055      29.735  27.317  24.101  1.00 16.73
ATOM   4008  O   ASN  1055      29.516  26.247  24.672  1.00 16.00
ATOM   4009  N   GLY  1056      30.450  27.394  22.980  1.00 15.99
ATOM   4010  CA  GLY  1056      30.956  26.167  22.380  1.00 10.17
ATOM   4011  C   GLY  1056      32.431  25.887  22.348  1.00  7.76
ATOM   4012  O   GLY  1056      33.090  25.836  23.370  1.00 10.46
ATOM   4013  N   GLY  1057      32.973  25.745  21.147  1.00 10.50
ATOM   4014  CA  GLY  1057      34.385  25.435  21.003  1.00  7.69
ATOM   4015  C   GLY  1057      34.523  24.142  20.195  1.00 13.35
ATOM   4016  O   GLY  1057      34.239  24.166  18.994  1.00 14.57
ATOM   4017  N   PRO  1058      34.761  22.991  20.838  1.00 12.99
ATOM   4018  CD  PRO  1058      35.011  21.753  20.057  1.00  8.59
ATOM   4019  CA  PRO  1058      34.898  22.727  22.263  1.00 12.12
ATOM   4020  CB  PRO  1058      34.920  21.193  22.318  1.00 10.19
ATOM   4021  CG  PRO  1058      35.678  20.849  21.083  1.00  9.66
ATOM   4022  C   PRO  1058      36.157  23.346  22.876  1.00 11.00
ATOM   4023  O   PRO  1058      37.205  23.415  22.224  1.00 13.72
ATOM   4024  N   GLY  1059      36.019  23.838  24.102  1.00  9.65
ATOM   4025  CA  GLY  1059      37.143  24.460  24.790  1.00  7.94
ATOM   4026  C   GLY  1059      37.040  25.981  24.896  1.00  4.39
```

FIG.23.70

ATOM	4027	O	GLY	1059	38.028	26.636	25.214	1.00	5.71	
ATOM	4028	N	CYS	1060	35.852	26.539	24.662	1.00	4.99	
ATOM	4029	CA	CYS	1060	35.680	27.991	24.724	1.00	9.20	
ATOM	4030	C	CYS	1060	34.762	28.409	25.871	1.00	10.91	
ATOM	4031	O	CYS	1060	33.866	27.662	26.276	1.00	12.21	
ATOM	4032	CB	CYS	1060	35.232	28.568	23.352	1.00	14.45	
ATOM	4033	SG	CYS	1060	36.421	28.285	21.964	1.00	12.15	
ATOM	4034	N	SER	1061	34.992	29.615	26.385	1.00	15.60	
ATOM	4035	CA	SER	1061	34.270	30.119	27.544	1.00	11.61	
ATOM	4036	CB	SER	1061	35.145	31.116	28.299	1.00	10.90	
ATOM	4037	OG	SER	1061	34.417	31.606	29.408	1.00	17.59	
ATOM	4038	C	SER	1061	32.876	30.716	27.414	1.00	10.67	
ATOM	4039	O	SER	1061	32.633	31.557	26.560	1.00	16.91	
ATOM	4040	N	SER	1062	31.994	30.351	28.348	1.00	8.64	
ATOM	4041	CA	SER	1062	30.643	30.886	28.382	1.00	7.49	
ATOM	4042	CB	SER	1062	29.753	29.979	29.188	1.00	6.06	
ATOM	4043	OG	SER	1062	29.863	28.669	28.670	1.00	8.98	
ATOM	4044	C	SER	1062	30.585	32.324	28.924	1.00	5.91	
ATOM	4045	O	SER	1062	29.516	32.937	28.979	1.00	9.24	
ATOM	4046	N	LEU	1063	31.737	32.851	29.336	1.00	9.64	
ATOM	4047	CA	LEU	1063	31.823	34.229	29.826	1.00	9.02	
ATOM	4048	CB	LEU	1063	33.047	34.445	30.734	1.00	6.16	
ATOM	4049	CG	LEU	1063	33.066	33.666	32.061	1.00	4.88	

FIG.23.71



```
ATOM   4050  CD1 LEU 1063      34.099  34.285  32.975  1.00  5.60
ATOM   4051  CD2 LEU 1063      31.694  33.633  32.731  1.00  2.93
ATOM   4052  C   LEU 1063      31.897  35.126  28.589  1.00 11.99
ATOM   4053  O   LEU 1063      31.962  36.356  28.694  1.00 13.19
ATOM   4054  N   ASP 1064      31.912  34.477  27.423  1.00 10.79
ATOM   4055  CA  ASP 1064      31.901  35.120  26.114  1.00  7.19
ATOM   4056  CB  ASP 1064      32.324  34.106  25.060  1.00 10.64
ATOM   4057  CG  ASP 1064      32.512  34.703  23.675  1.00 13.89
ATOM   4058  OD1 ASP 1064      32.354  35.921  23.493  1.00 16.35
ATOM   4059  OD2 ASP 1064      32.825  33.939  22.739  1.00 22.07
ATOM   4060  C   ASP 1064      30.437  35.499  25.932  1.00  4.32
ATOM   4061  O   ASP 1064      30.110  36.621  25.581  1.00 11.79
ATOM   4062  N   GLY 1065      29.555  34.556  26.225  1.00  6.64
ATOM   4063  CA  GLY 1065      28.127  34.805  26.140  1.00  5.27
ATOM   4064  C   GLY 1065      27.684  35.909  27.099  1.00 13.37
ATOM   4065  O   GLY 1065      26.712  36.626  26.830  1.00 13.24
ATOM   4066  N   LEU 1066      28.348  36.037  28.244  1.00 14.86
ATOM   4067  CA  LEU 1066      27.987  37.090  29.198  1.00 10.38
ATOM   4068  CB  LEU 1066      28.482  36.762  30.624  1.00  9.13
ATOM   4069  CG  LEU 1066      27.974  37.632  31.800  1.00  5.95
ATOM   4070  CD1 LEU 1066      28.104  36.843  33.076  1.00  9.17
ATOM   4071  CD2 LEU 1066      28.720  38.961  31.951  1.00  5.24
ATOM   4072  C   LEU 1066      28.525  38.451  28.786  1.00 10.31
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FIG.23.72

```
ATOM   4073  O   LEU 1066      27.758  39.362  28.495  1.00 10.99
ATOM   4074  N   LEU 1067      29.844  38.547  28.722  1.00  9.76
ATOM   4075  CA  LEU 1067      30.532  39.789  28.423  1.00 13.61
ATOM   4076  CB  LEU 1067      32.006  39.671  28.846  1.00  7.85
ATOM   4077  CG  LEU 1067      32.314  39.574  30.347  1.00  8.30
ATOM   4078  CD1 LEU 1067      33.807  39.475  30.541  1.00  6.09
ATOM   4079  CD2 LEU 1067      31.760  40.789  31.082  1.00  5.02
ATOM   4080  C   LEU 1067      30.480  40.351  27.022  1.00 15.33
ATOM   4081  O   LEU 1067      30.828  41.515  26.824  1.00 13.42
ATOM   4082  N   THR 1068      30.153  39.523  26.037  1.00 16.95
ATOM   4083  CA  THR 1068      30.132  40.000  24.651  1.00 12.20
ATOM   4084  CB  THR 1068      31.269  39.397  23.791  1.00 11.32
ATOM   4085  OG1 THR 1068      30.861  38.122  23.290  1.00 22.22
ATOM   4086  CG2 THR 1068      32.544  39.192  24.601  1.00  6.13
ATOM   4087  C   THR 1068      28.832  39.737  23.911  1.00  9.29
ATOM   4088  O   THR 1068      28.621  40.312  22.853  1.00  8.35
ATOM   4089  N   GLU 1069      27.964  38.879  24.455  1.00  9.66
ATOM   4090  CA  GLU 1069      26.713  38.579  23.779  1.00  2.87
ATOM   4091  CB  GLU 1069      26.603  37.092  23.474  1.00  2.00
ATOM   4092  CG  GLU 1069      27.747  36.517  22.732  1.00  2.00
ATOM   4093  CD  GLU 1069      27.440  35.072  22.388  1.00 10.44
ATOM   4094  OE1 GLU 1069      28.014  34.140  22.979  1.00 13.18
ATOM   4095  OE2 GLU 1069      26.540  34.866  21.568  1.00  7.99
```

FIG.23.73

```
ATOM   4096  C   GLU 1069      25.432  39.016  24.453  1.00  8.48
ATOM   4097  O   GLU 1069      24.713  39.883  23.946  1.00 12.89
ATOM   4098  N   HIS 1070      25.075  38.356  25.548  1.00  7.61
ATOM   4099  CA  HIS 1070      23.827  38.713  26.204  1.00  7.18
ATOM   4100  CB  HIS 1070      22.664  37.820  25.691  1.00 12.98
ATOM   4101  CG  HIS 1070      22.907  36.344  25.802  1.00 15.52
ATOM   4102  CD2 HIS 1070      22.567  35.319  24.987  1.00 12.57
ATOM   4103  ND1 HIS 1070      23.563  35.767  26.874  1.00 20.02
ATOM   4104  CE1 HIS 1070      23.609  34.458  26.711  1.00 10.15
ATOM   4105  NE2 HIS 1070      23.014  34.164  25.574  1.00 14.92
ATOM   4106  C   HIS 1070      23.816  38.902  27.733  1.00  9.42
ATOM   4107  O   HIS 1070      22.759  38.806  28.379  1.00 11.06
ATOM   4108  N   GLY 1071      24.988  39.196  28.291  1.00 12.09
ATOM   4109  CA  GLY 1071      25.060  39.442  29.711  1.00 15.45
ATOM   4110  C   GLY 1071      24.440  40.792  30.089  1.00 17.58
ATOM   4111  O   GLY 1071      24.138  41.618  29.200  1.00 11.30
ATOM   4112  N   PRO 1072      24.226  41.043  31.406  1.00 16.14
ATOM   4113  CD  PRO 1072      24.537  40.154  32.538  1.00 11.01
ATOM   4114  CA  PRO 1072      23.629  42.305  31.886  1.00 14.40
ATOM   4115  CB  PRO 1072      23.425  42.029  33.379  1.00 11.56
ATOM   4116  CG  PRO 1072      24.565  41.112  33.699  1.00 13.32
ATOM   4117  C   PRO 1072      24.484  43.541  31.600  1.00 11.41
ATOM   4118  O   PRO 1072      23.985  44.675  31.625  1.00 14.15
```

FIG.23.74

ATOM	4119	N	PHE	1073	25.757	43.308	31.304	1.00	10.67	
ATOM	4120	CA	PHE	1073	26.719	44.350	30.958	1.00	11.47	
ATOM	4121	CB	PHE	1073	27.452	44.906	32.194	1.00	14.42	
ATOM	4122	CG	PHE	1073	27.569	43.926	33.341	1.00	12.17	
ATOM	4123	CD1	PHE	1073	26.753	44.067	34.460	1.00	11.62	
ATOM	4124	CD2	PHE	1073	28.462	42.849	33.280	1.00	12.34	
ATOM	4125	CE1	PHE	1073	26.815	43.152	35.501	1.00	9.61	
ATOM	4126	CE2	PHE	1073	28.536	41.926	34.312	1.00	14.52	
ATOM	4127	CZ	PHE	1073	27.704	42.076	35.432	1.00	11.76	
ATOM	4128	C	PHE	1073	27.710	43.707	29.994	1.00	11.39	
ATOM	4129	O	PHE	1073	27.894	42.494	30.008	1.00	11.75	
ATOM	4130	N	LEU	1074	28.369	44.521	29.182	1.00	13.78	
ATOM	4131	CA	LEU	1074	29.302	44.007	28.198	1.00	13.58	
ATOM	4132	CB	LEU	1074	28.725	44.228	26.794	1.00	10.75	
ATOM	4133	CG	LEU	1074	27.320	43.656	26.597	1.00	9.26	
ATOM	4134	CD1	LEU	1074	26.733	44.121	25.289	1.00	13.37	
ATOM	4135	CD2	LEU	1074	27.371	42.133	26.651	1.00	7.69	
ATOM	4136	C	LEU	1074	30.594	44.742	28.330	1.00	13.92	
ATOM		O	LEU	1074	30.588	45.934	28.585	1.00	15.49	
ATOM			VAL	1075	31.704	44.036	28.182	1.00	12.83	
ATOM				1075	33.037	43	90	1.00	15.13	
ATOM			VAL	1075	34.157	4	3.414	1.00	16.03	
ATOM		CG1	VAL	1075	34.194	42	27.197	1.00	15.81	

FIG.23.75

```
ATOM   4142  CG2 VAL  1075      35.499  44.270  28.604  1.00 12.30
ATOM   4143  C   VAL  1075      33.206  45.579  27.098  1.00 17.47
ATOM   4144  O   VAL  1075      32.715  45.328  25.987  1.00 17.39
ATOM   4145  N   GLN  1076      33.928  46.663  27.340  1.00 17.37
ATOM   4146  CA  GLN  1076      34.189  47.660  26.327  1.00 14.53
ATOM   4147  CB  GLN  1076      34.018  49.062  26.944  1.00 19.73
ATOM   4148  CG  GLN  1076      32.615  49.311  27.499  1.00 16.49
ATOM   4149  CD  GLN  1076      31.532  49.111  26.450  1.00 20.70
ATOM   4150  OE1 GLN  1076      31.431  49.886  25.510  1.00 27.97
ATOM   4151  NE2 GLN  1076      30.719  48.086  26.614  1.00 20.69
ATOM   4152  C   GLN  1076      35.568  47.472  25.755  1.00 13.22
ATOM   4153  O   GLN  1076      36.375  46.721  26.301  1.00 14.01
=======================================================================
ATOM   4697  N   LEU  1144      13.206  25.412  34.159  1.00 13.22
ATOM   4698  CA  LEU  1144      14.571  25.382  33.699  1.00 13.56
ATOM   4699  CB  LEU  1144      15.264  24.198  34.367  1.00 10.34
ATOM   4700  CG  LEU  1144      16.655  23.779  33.916  1.00  8.49
ATOM   4701  CD1 LEU  1144      17.704  24.805  34.343  1.00  5.67
ATOM   4702  CD2 LEU  1144      16.958  22.392  34.498  1.00 10.36
ATOM   4703  C   LEU  1144      14.628  25.232  32.175  1.00 16.10
ATOM   4704  O   LEU  1144      13.863  24.469  31.588  1.00 18.50
ATOM   4705  N   PHE  1145      15.544  25.957  31.542  1.00 16.40
ATOM   4706  CA  PHE  1145      15.722  25.895  30.098  1.00 13.20
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FIG:23.76

```
ATOM   4707  CB  PHE  1145      15.246  27.192  29.436  1.00 14.23
ATOM   4708  CG  PHE  1145      13.755  27.350  29.421  1.00 16.54
ATOM   4709  CD1 PHE  1145      13.090  27.958  30.485  1.00 17.20
ATOM   4710  CD2 PHE  1145      13.008  26.900  28.343  1.00 16.49
ATOM   4711  CE1 PHE  1145      11.698  28.112  30.471  1.00 15.56
ATOM   4712  CE2 PHE  1145      11.612  27.053  28.318  1.00 14.48
ATOM   4713  CZ  PHE  1145      10.958  27.658  29.383  1.00 16.77
ATOM   4714  C   PHE  1145      17.208  25.733  29.892  1.00 14.21
ATOM   4715  O   PHE  1145      17.990  26.336  30.638  1.00 15.28
ATOM   4716  N   LEU  1146      17.606  24.859  28.972  1.00 13.91
ATOM   4717  CA  LEU  1146      19.032  24.646  28.685  1.00 10.47
ATOM   4718  CB  LEU  1146      19.352  23.134  28.658  1.00  9.43
ATOM   4719  CG  LEU  1146      18.791  22.331  29.855  1.00  9.20
ATOM   4720  CD1 LEU  1146      18.952  20.829  29.653  1.00  8.44
ATOM   4721  CD2 LEU  1146      19.519  22.741  31.125  1.00  5.27
ATOM   4722  C   LEU  1146      19.318  25.338  27.324  1.00 10.63
ATOM   4723  O   LEU  1146      18.695  25.011  26.318  1.00 10.44
ATOM   4724  N   THR  1147      20.214  26.325  27.315  1.00 14.19
ATOM   4725  CA  THR  1147      20.537  27.090  26.113  1.00  9.23
ATOM   4726  CB  THR  1147      19.914  28.551  26.148  1.00  5.47
ATOM   4727  OG1 THR  1147      20.546  29.352  27.154  1.00 10.68
ATOM   4728  CG2 THR  1147      18.449  28.512  26.411  1.00  2.00
ATOM   4729  C   THR  1147      22.038  27.176  25.859  1.00  8.62
```

FIG.23.77

```
ATOM   4730  O   THR  1147      22.843  27.037  26.781  1.00  9.01
ATOM   4731  N   GLY  1148      22.419  27.406  24.603  1.00  7.75
ATOM   4732  CA  GLY  1148      23.829  27.484  24.272  1.00  3.58
ATOM   4733  C   GLY  1148      24.059  27.842  22.824  1.00  4.46
ATOM   4734  O   GLY  1148      23.128  28.015  22.049  1.00  3.11
ATOM   4735  N   GLU  1149      25.304  27.808  22.413  1.00  7.23
ATOM   4736  CA  GLU  1149      25.627  28.188  21.066  1.00  9.10
ATOM   4737  CB  GLU  1149      26.010  29.673  21.109  1.00  7.91
ATOM   4738  CG  GLU  1149      26.471  30.328  19.819  1.00  4.32
ATOM   4739  CD  GLU  1149      27.043  31.704  20.104  1.00  3.75
ATOM   4740  OE1 GLU  1149      28.288  31.863  20.114  1.00  5.72
ATOM   4741  OE2 GLU  1149      26.236  32.626  20.338  1.00  8.13
ATOM   4742  C   GLU  1149      26.788  27.406  20.486  1.00  7.02
ATOM   4743  O   GLU  1149      27.669  26.958  21.220  1.00 11.07
ATOM   4744  N   SER  1150      26.762  27.246  19.160  1.00  7.15
ATOM   4745  CA  SER  1150      27.841  26.611  18.408  1.00  4.85
ATOM   4746  CB  SER  1150      29.103  27.442  18.628  1.00  3.37
ATOM   4747  OG  SER  1150      30.153  27.159  17.725  1.00 14.60
ATOM   4748  C   SER  1150      28.032  25.143  18.779  1.00  6.96
ATOM   4749  O   SER  1150      27.137  24.326  18.535  1.00  6.55
ATOM   4750  N   TYR  1151      29.148  24.798  19.415  1.00  7.04
ATOM   4751  CA  TYR  1151      29.366  23.400  19.796  1.00  7.55
ATOM   4752  CB  TYR  1151      30.781  23.140  20.272  1.00  9.49
```

FIG.23.78

```
ATOM   4753  CG  TYR  1151      31.118  21.671  20.242  1.00 15.57
ATOM   4754  CD1 TYR  1151      31.584  21.073  19.075  1.00 14.31
ATOM   4755  CE1 TYR  1151      31.839  19.721  19.021  1.00 13.43
ATOM   4756  CD2 TYR  1151      30.924  20.864  21.362  1.00 15.31
ATOM   4757  CE2 TYR  1151      31.172  19.509  21.315  1.00 11.83
ATOM   4758  CZ  TYR  1151      31.623  18.943  20.142  1.00 13.92
ATOM   4759  OH  TYR  1151      31.811  17.595  20.059  1.00  9.48
ATOM   4760  C   TYR  1151      28.369  22.966  20.853  1.00  6.75
ATOM   4761  O   TYR  1151      28.084  21.778  20.974  1.00 13.35
ATOM   4762  N   ALA  1152      27.788  23.929  21.577  1.00  5.99
ATOM   4763  CA  ALA  1152      26.767  23.616  22.559  1.00  2.00
ATOM   4764  CB  ALA  1152      26.383  24.820  23.321  1.00  4.52
ATOM   4765  C   ALA  1152      25.553  23.032  21.857  1.00  4.59
ATOM   4766  O   ALA  1152      24.548  22.702  22.493  1.00  5.46
ATOM   4767  N   GLY  1153      25.605  22.953  20.530  1.00  7.41
ATOM   4768  CA  GLY  1153      24.507  22.360  19.800  1.00  2.72
ATOM   4769  C   GLY  1153      24.631  20.862  20.044  1.00  5.28
ATOM   4770  O   GLY  1153      23.700  20.112  19.769  1.00  8.08
ATOM   4771  N   ILE  1154      25.833  20.442  20.443  1.00  8.44
ATOM   4772  CA  ILE  1154      26.130  19.057  20.827  1.00  8.33
ATOM   4773  CB  ILE  1154      27.600  18.690  20.531  1.00  8.67
ATOM   4774  CG2 ILE  1154      27.908  17.283  21.043  1.00  2.60
ATOM   4775  CG1 ILE  1154      27.941  18.880  19.037  1.00  8.20
```

FIG.23.79

ATOM	4776	CD1	ILE	1154	27.561	17.739	18.132	1.00	9.74
ATOM	4777	C	ILE	1154	25.914	18.990	22.363	1.00	10.50
ATOM	4778	O	ILE	1154	25.100	18.194	22.844	1.00	12.69
ATOM	4779	N	TYR	1155	26.624	19.857	23.107	1.00	12.77
ATOM	4780	CA	TYR	1155	26.518	19.961	24.578	1.00	11.74
ATOM	4781	CB	TYR	1155	27.161	21.253	25.132	1.00	3.22
ATOM	4782	CG	TYR	1155	28.662	21.395	25.000	1.00	2.00
ATOM	4783	CD1	TYR	1155	29.253	22.658	24.927	1.00	2.74
ATOM	4784	CE1	TYR	1155	30.635	22.802	24.824	1.00	2.40
ATOM	4785	CD2	TYR	1155	29.486	20.285	24.964	1.00	4.07
ATOM	4786	CE2	TYR	1155	30.869	20.416	24.855	1.00	3.82
ATOM	4787	CZ	TYR	1155	31.439	21.670	24.793	1.00	2.00
ATOM	4788	OH	TYR	1155	32.819	21.785	24.754	1.00	3.24
ATOM	4789	C	TYR	1155	25.075	19.965	25.066	1.00	12.15
ATOM	4790	O	TYR	1155	24.698	19.119	25.870	1.00	18.34
ATOM	4919	N	GLY	1173	12.464	23.418	28.523	1.00	12.94
ATOM	4920	CA	GLY	1173	12.808	23.564	27.126	1.00	12.85
ATOM	4921	C	GLY	1173	14.259	23.786	26.878	1.00	10.63
ATOM	4922	O	GLY	1173	15.052	23.822	27.820	1.00	15.71
ATOM	4923	N	LEU	1174	14.605	23.920	25.606	1.00	15.11
ATOM	4924	CA	LEU	1174	15.986	24.147	25.181	1.00	17.83
ATOM	4925	CB	LEU	1174	16.753	22.808	25.033	1.00	18.83

FIG.23.80

ATOM	4926	CG	LEU	1174	16.324	21.627	24.139	1.00	21.15	
ATOM	4927	CD1	LEU	1174	17.570	20.903	23.670	1.00	18.66	
ATOM	4928	CD2	LEU	1174	15.384	20.660	24.875	1.00	16.90	
ATOM	4929	C	LEU	1174	16.066	24.978	23.891	1.00	16.86	
ATOM	4930	O	LEU	1174	15.197	24.872	23.032	1.00	16.96	
ATOM	4931	N	ALA	1175	17.117	25.785	23.757	1.00	16.09	
ATOM	4932	CA	ALA	1175	17.315	26.636	22.584	1.00	13.66	
ATOM	4933	CB	ALA	1175	16.831	28.064	22.877	1.00	10.96	
ATOM	4934	C	ALA	1175	18.808	26.626	22.238	1.00	11.09	
ATOM	4935	O	ALA	1175	19.646	26.733	23.128	1.00	9.89	
ATOM	4936	N	VAL	1176	19.136	26.429	20.961	1.00	8.95	
ATOM	4937	CA	VAL	1176	20.527	26.368	20.507	1.00	9.56	
ATOM	4938	CB	VAL	1176	20.881	24.923	20.037	1.00	11.73	
ATOM	4939	CG1	VAL	1176	22.204	24.905	19.271	1.00	5.65	
ATOM	4940	CG2	VAL	1176	20.971	23.991	21.227	1.00	8.28	
ATOM	4941	C	VAL	1176	20.754	27.340	19.342	1.00	11.14	
ATOM	4942	O	VAL	1176	20.033	27.277	18.350	1.00	11.32	
ATOM	4943	N	GLY	1177	21.747	28.222	19.454	1.00	14.54	
ATOM	4944	CA	GLY	1177	22.020	29.172	18.384	1.00	10.12	
ATOM	4945	C	GLY	1177	23.123	28.723	17.463	1.00	8.78	
ATOM	4946	O	GLY	1177	24.217	28.404	17.930	1.00	4.07	
ATOM	4947	N	ASN	1178	22.871	28.722	16.162	1.00	8.51	
ATOM	4948	CA	ASN	1178	23.891	28.266	15.205	1.00	5.20	

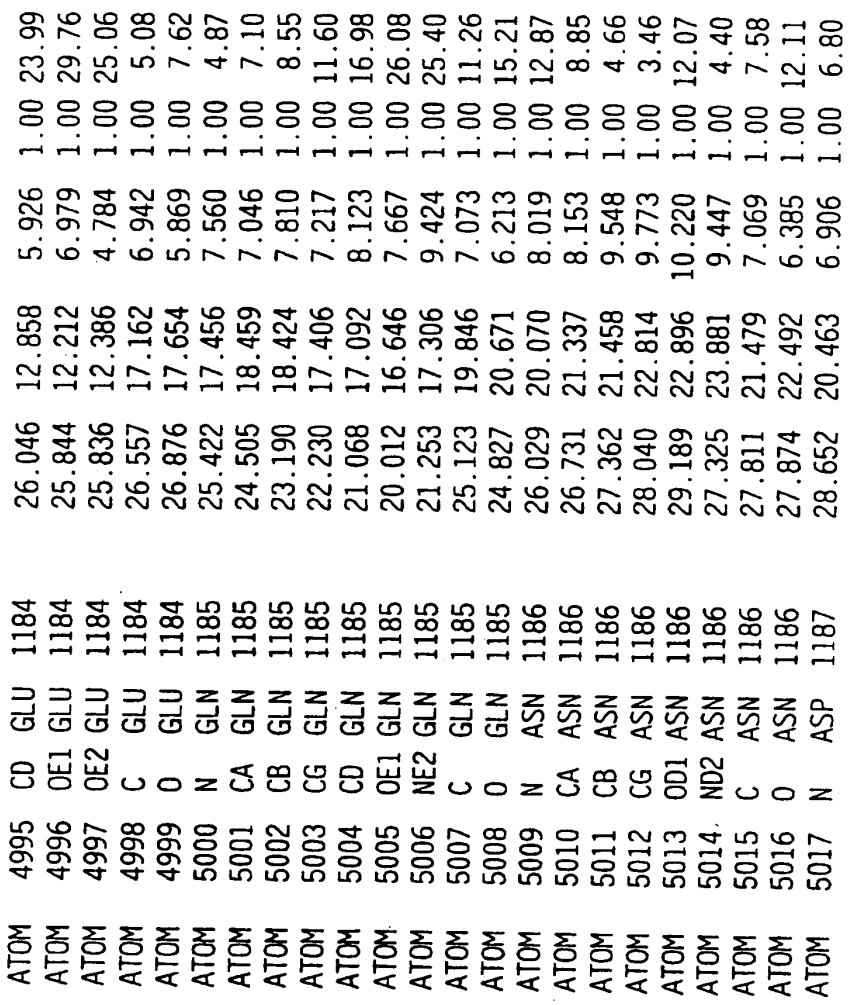
FIG.23.81

ATOM	4949	CB	ASN	1178	24.882	29.381	14.874	1.00	6.09
ATOM	4950	CG	ASN	1178	24.253	30.496	14.080	1.00	10.75
ATOM	4951	OD1	ASN	1178	23.518	31.319	14.632	1.00	9.79
ATOM	4952	ND2	ASN	1178	24.485	30.503	12.766	1.00	10.54
ATOM	4953	C	ASN	1178	24.642	27.062	15.770	1.00	2.90
ATOM	4954	O	ASN	1178	25.867	27.062	15.864	1.00	4.70
ATOM	4955	N	GLY	1179	23.895	26.031	16.128	1.00	7.96
ATOM	4956	CA	GLY	1179	24.520	24.867	16.717	1.00	13.63
ATOM	4957	C	GLY	1179	24.984	23.838	15.723	1.00	14.42
ATOM	4958	O	GLY	1179	24.437	23.747	14.630	1.00	17.43
ATOM	4959	N	LEU	1180	25.982	23.056	16.129	1.00	11.44
ATOM	4960	CA	LEU	1180	26.549	21.979	15.324	1.00	7.41
ATOM	4961	CB	LEU	1180	27.971	21.716	15.766	1.00	8.30
ATOM	4962	CG	LEU	1180	28.874	20.795	14.975	1.00	12.32
ATOM	4963	CD1	LEU	1180	29.132	21.344	13.594	1.00	11.76
ATOM	4964	CD2	LEU	1180	30.162	20.722	15.743	1.00	7.94
ATOM	4965	C	LEU	1180	25.726	20.736	15.588	1.00	10.39
ATOM	4966	O	LEU	1180	26.137	19.888	16.357	1.00	20.58
ATOM	4967	N	SER	1181	24.562	20.641	14.954	1.00	7.38
ATOM	4968	CA	SER	1181	23.665	19.505	15.117	1.00	5.37
ATOM	4969	CB	SER	1181	22.252	19.919	14.728	1.00	3.06
ATOM	4970	OG	SER	1181	21.898	21.130	15.352	1.00	8.63
ATOM	4971	C	SER	1181	24.088	18.253	14.336	1.00	7.63

FIG.23.82

```
ATOM   4972  O   SER 1181      23.870  17.149  14.773  1.00  9.69
ATOM   4973  N   SER 1182      24.681  18.446  13.171  1.00 13.08
ATOM   4974  CA  SER 1182      25.129  17.359  12.326  1.00  9.50
ATOM   4975  CB  SER 1182      23.999  16.922  11.392  1.00 11.96
ATOM   4976  OG  SER 1182      24.484  16.052  10.380  1.00 13.63
ATOM   4977  C   SER 1182      26.284  17.862  11.496  1.00 11.32
ATOM   4978  O   SER 1182      26.147  18.831  10.753  1.00 11.11
ATOM   4979  N   TYR 1183      27.433  17.216  11.639  1.00  8.38
ATOM   4980  CA  TYR 1183      28.638  17.577  10.892  1.00  7.66
ATOM   4981  CB  TYR 1183      29.815  16.711  11.324  1.00  6.76
ATOM   4982  CG  TYR 1183      30.179  16.800  12.795  1.00 10.68
ATOM   4983  CD1 TYR 1183      29.492  16.044  13.753  1.00 10.39
ATOM   4984  CE1 TYR 1183      29.837  16.105  15.104  1.00 13.19
ATOM   4985  CD2 TYR 1183      31.216  17.617  13.223  1.00  3.47
ATOM   4986  CE2 TYR 1183      31.568  17.688  14.582  1.00  8.20
ATOM   4987  CZ  TYR 1183      30.875  16.929  15.515  1.00  4.50
ATOM   4988  OH  TYR 1183      31.224  17.007  16.840  1.00  8.71
ATOM   4989  C   TYR 1183      28.427  17.396  9.394  1.00 11.19
ATOM   4990  O   TYR 1183      28.933  18.157  8.604  1.00 16.20
ATOM   4991  N   GLU 1184      27.681  16.374  9.006  1.00 11.16
ATOM   4992  CA  GLU 1184      27.427  16.102  7.595  1.00  9.88
ATOM   4993  CB  GLU 1184      26.762  14.734  7.455  1.00 13.18
ATOM   4994  CG  GLU 1184      26.589  14.271  6.029  1.00 22.28
```

FIG.23.83



```
ATOM   4995  CD  GLU 1184      26.046  12.858   5.926  1.00 23.99
ATOM   4996  OE1 GLU 1184      25.844  12.212   6.979  1.00 29.76
ATOM   4997  OE2 GLU 1184      25.836  12.386   4.784  1.00 25.06
ATOM   4998  C   GLU 1184      26.557  17.162   6.942  1.00  5.08
ATOM   4999  O   GLU 1184      26.876  17.654   5.869  1.00  7.62
ATOM   5000  N   GLN 1185      25.422  17.456   7.560  1.00  4.87
ATOM   5001  CA  GLN 1185      24.505  18.459   7.046  1.00  7.10
ATOM   5002  CB  GLN 1185      23.190  18.424   7.810  1.00  8.55
ATOM   5003  CG  GLN 1185      22.230  17.406   7.217  1.00 11.60
ATOM   5004  CD  GLN 1185      21.068  17.092   8.123  1.00 16.98
ATOM   5005  OE1 GLN 1185      20.012  16.646   7.667  1.00 26.08
ATOM   5006  NE2 GLN 1185      21.253  17.306   9.424  1.00 25.40
ATOM   5007  C   GLN 1185      25.123  19.846   7.073  1.00 11.26
ATOM   5008  O   GLN 1185      24.827  20.671   6.213  1.00 15.21
ATOM   5009  N   ASN 1186      26.029  20.070   8.019  1.00 12.87
ATOM   5010  CA  ASN 1186      26.731  21.337   8.153  1.00  8.85
ATOM   5011  CB  ASN 1186      27.362  21.458   9.548  1.00  4.66
ATOM   5012  CG  ASN 1186      28.040  22.814   9.773  1.00  3.46
ATOM   5013  OD1 ASN 1186      29.189  22.896  10.220  1.00 12.07
ATOM   5014  ND2 ASN 1186      27.325  23.881   9.447  1.00  4.40
ATOM   5015  C   ASN 1186      27.811  21.479   7.069  1.00  7.58
ATOM   5016  O   ASN 1186      27.874  22.492   6.385  1.00 12.11
ATOM   5017  N   ASP 1187      28.652  20.463   6.906  1.00  6.80
```

FIG.23.84

```
ATOM   5018  CA  ASP  1187      29.722  20.500   5.907  1.00  6.70
ATOM   5019  CB  ASP  1187      30.589  19.253   5.985  1.00 10.91
ATOM   5020  CG  ASP  1187      31.414  19.182   7.256  1.00 14.86
ATOM   5021  OD1 ASP  1187      31.598  20.223   7.929  1.00 14.90
ATOM   5022  OD2 ASP  1187      31.892  18.062   7.570  1.00 16.93
ATOM   5023  C   ASP  1187      29.178  20.612   4.490  1.00 11.55
ATOM   5024  O   ASP  1187      29.749  21.331   3.675  1.00 13.94
ATOM   5025  N   ASN  1188      28.123  19.851   4.187  1.00  8.53
ATOM   5026  CA  ASN  1188      27.484  19.876   2.863  1.00  9.33
ATOM   5027  CB  ASN  1188      26.418  18.784   2.725  1.00  4.69
ATOM   5028  CG  ASN  1188      27.000  17.387   2.563  1.00  6.21
ATOM   5029  OD1 ASN  1188      28.105  17.195   2.045  1.00 11.05
ATOM   5030  ND2 ASN  1188      26.232  16.397   2.989  1.00  9.02
ATOM   5031  C   ASN  1188      26.805  21.222   2.549  1.00  9.45
ATOM   5032  O   ASN  1188      27.022  21.777   1.482  1.00 12.60
ATOM   5033  N   SER  1189      25.922  21.694   3.434  1.00 12.40
ATOM   5034  CA  SER  1189      25.213  22.976   3.234  1.00  8.14
ATOM   5035  CB  SER  1189      24.209  23.248   4.369  1.00 11.33
ATOM   5036  OG  SER  1189      24.838  23.336   5.639  1.00 14.66
ATOM   5037  C   SER  1189      26.163  24.172   3.066  1.00  5.20
ATOM   5038  O   SER  1189      25.848  25.107   2.341  1.00 10.13
ATOM   5039  N   LEU  1190      27.321  24.108   3.726  1.00  4.88
ATOM   5040  CA  LEU  1190      28.347  25.144   3.676  1.00  7.24
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FIG.23.85

```
ATOM  5041  CB  LEU 1190      29.492  24.841   4.660  1.00  5.16
ATOM  5042  CG  LEU 1190      30.769  25.694   4.538  1.00  4.08
ATOM  5043  CD1 LEU 1190      30.472  27.146   4.898  1.00  8.34
ATOM  5044  CD2 LEU 1190      31.844  25.167   5.418  1.00  5.42
ATOM  5045  C   LEU 1190      28.958  25.322   2.304  1.00 12.23
ATOM  5046  O   LEU 1190      29.261  26.448   1.910  1.00 14.63
ATOM  5047  N   VAL 1191      29.240  24.209   1.617  1.00 11.86
ATOM  5048  CA  VAL 1191      29.818  24.294   0.283  1.00  7.71
ATOM  5049  CB  VAL 1191      30.236  22.927  -0.261  1.00 10.40
ATOM  5050  CG1 VAL 1191      30.927  23.113  -1.605  1.00  5.34
ATOM  5051  CG2 VAL 1191      31.255  22.298   0.683  1.00  2.48
ATOM  5052  C   VAL 1191      28.826  25.015  -0.621  1.00  6.93
ATOM  5053  O   VAL 1191      29.202  25.900  -1.367  1.00  9.05
ATOM  5054  N   TYR 1192      27.555  24.669  -0.503  1.00  7.63
ATOM  5055  CA  TYR 1192      26.493  25.330  -1.249  1.00 11.42
ATOM  5056  CB  TYR 1192      25.172  24.681  -0.884  1.00 14.20
ATOM  5057  CG  TYR 1192      24.927  23.392  -1.587  1.00 19.34
ATOM  5058  CD1 TYR 1192      25.410  22.187  -1.091  1.00 18.62
ATOM  5059  CE1 TYR 1192      25.175  21.003  -1.763  1.00 19.90
ATOM  5060  CD2 TYR 1192      24.206  23.377  -2.763  1.00 20.70
ATOM  5061  CE2 TYR 1192      23.964  22.209  -3.440  1.00 16.84
ATOM  5062  CZ  TYR 1192      24.441  21.028  -2.946  1.00 18.91
ATOM  5063  OH  TYR 1192      24.141  19.892  -3.653  1.00 19.39
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FIG.23.86

```
ATOM   5064  C   TYR  1192      26.413  26.827  -0.851  1.00 15.42
ATOM   5065  O   TYR  1192      26.256  27.713  -1.696  1.00 13.38
ATOM   5066  N   PHE  1193      26.395  27.076   0.455  1.00 12.57
ATOM   5067  CA  PHE  1193      26.346  28.419   1.014  1.00 10.64
ATOM   5068  CB  PHE  1193      26.592  28.348   2.545  1.00  7.63
ATOM   5069  CG  PHE  1193      26.377  29.653   3.262  1.00  5.57
ATOM   5070  CD1 PHE  1193      25.185  29.901   3.928  1.00  3.60
ATOM   5071  CD2 PHE  1193      27.350  30.652   3.233  1.00  3.09
ATOM   5072  CE1 PHE  1193      24.960  31.138   4.559  1.00  5.95
ATOM   5073  CE2 PHE  1193      27.134  31.885   3.851  1.00  2.00
ATOM   5074  CZ  PHE  1193      25.941  32.125   4.513  1.00  2.00
ATOM   5075  C   PHE  1193      27.419  29.267   0.337  1.00  4.40
ATOM   5076  O   PHE  1193      27.135  30.351  -0.159  1.00  7.94
ATOM   5077  N   ALA  1194      28.640  28.749   0.298  1.00  2.95
ATOM   5078  CA  ALA  1194      29.783  29.440  -0.292  1.00  5.66
ATOM   5079  CB  ALA  1194      31.050  28.646  -0.098  1.00  4.86
ATOM   5080  C   ALA  1194      29.624  29.831  -1.765  1.00 10.74
ATOM   5081  O   ALA  1194      30.001  30.935  -2.147  1.00 12.73
ATOM   5082  N   TYR  1195      29.114  28.936  -2.609  1.00 12.02
ATOM   5083  CA  TYR  1195      28.940  29.297  -4.007  1.00  9.05
ATOM   5084  CB  TYR  1195      28.530  28.086  -4.850  1.00 12.04
ATOM   5085  CG  TYR  1195      28.251  28.445  -6.310  1.00  7.57
ATOM   5086  CD1 TYR  1195      29.250  29.024  -7.113  1.00  2.00
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FIG.23.87

```
ATOM   5087  CE1 TYR  1195      29.007  29.342  -8.466  1.00  3.93
ATOM   5088  CD2 TYR  1195      26.996  28.188  -6.887  1.00  4.93
ATOM   5089  CE2 TYR  1195      26.739  28.488  -8.242  1.00 12.14
ATOM   5090  CZ  TYR  1195      27.756  29.064  -9.026  1.00  5.79
ATOM   5091  OH  TYR  1195      27.526  29.304 -10.363  1.00  7.94
ATOM   5092  C   TYR  1195      27.889  30.384  -4.175  1.00  7.65
ATOM   5093  O   TYR  1195      28.108  31.366  -4.870  1.00 13.56
ATOM   5094  N   TYR  1196      26.742  30.194  -3.541  1.00  4.57
ATOM   5095  CA  TYR  1196      25.638  31.115  -3.652  1.00  5.37
ATOM   5096  CB  TYR  1196      24.358  30.406  -3.290  1.00  5.49
ATOM   5097  CG  TYR  1196      24.031  29.328  -4.306  1.00 12.37
ATOM   5098  CD1 TYR  1196      24.480  28.014  -4.134  1.00  7.05
ATOM   5099  CE1 TYR  1196      24.208  27.030  -5.068  1.00  9.49
ATOM   5100  CD2 TYR  1196      23.296  29.626  -5.451  1.00 12.25
ATOM   5101  CE2 TYR  1196      23.014  28.657  -6.392  1.00 13.86
ATOM   5102  CZ  TYR  1196      23.473  27.356  -6.199  1.00 15.48
ATOM   5103  OH  TYR  1196      23.192  26.397  -7.144  1.00 17.66
ATOM   5104  C   TYR  1196      25.778  32.445  -2.949  1.00  8.50
ATOM   5105  O   TYR  1196      24.955  33.333  -3.137  1.00 10.82
ATOM   5106  N   HIS  1197      26.815  32.567  -2.127  1.00  9.62
ATOM   5107  CA  HIS  1197      27.114  33.807  -1.414  1.00  6.06
ATOM   5108  CB  HIS  1197      27.325  33.566   0.079  1.00  2.90
ATOM   5109  CG  HIS  1197      26.050  33.370   0.825  1.00  2.00
```

FIG.23.88

```
ATOM   5110  CD2 HIS  1197      25.331  34.214   1.598  1.00  2.00
ATOM   5111  ND1 HIS  1197      25.295  32.224   0.717  1.00  2.00
ATOM   5112  CE1 HIS  1197      24.160  32.371   1.376  1.00  2.00
ATOM   5113  NE2 HIS  1197      24.162  33.573   1.923  1.00  2.00
ATOM   5114  C   HIS  1197      28.336  34.424  -2.085  1.00  8.83
ATOM   5115  O   HIS  1197      28.984  35.305  -1.538  1.00 15.06
==========================================================================
ATOM   5341  N   LEU  1226      39.631  11.780  -5.534  1.00 15.25
ATOM   5342  CA  LEU  1226      40.781  12.643  -5.687  1.00 23.06
ATOM   5343  CB  LEU  1226      41.769  11.961  -6.604  1.00 26.67
ATOM   5344  CG  LEU  1226      43.087  11.890  -5.864  1.00 35.66
ATOM   5345  CD1 LEU  1226      43.737  10.548  -6.101  1.00 38.32
ATOM   5346  CD2 LEU  1226      43.966  13.069  -6.308  1.00 35.54
ATOM   5347  C   LEU  1226      40.616  14.131  -6.071  1.00 25.04
ATOM   5348  O   LEU  1226      41.053  15.016  -5.338  1.00 27.76
ATOM   5349  N   GLU  1227      40.022  14.426  -7.221  1.00 25.04
ATOM   5350  CA  GLU  1227      39.878  15.831  -7.600  1.00 24.73
ATOM   5351  CB  GLU  1227      39.645  16.003  -9.110  1.00 32.37
ATOM   5352  CG  GLU  1227      40.211  17.335  -9.681  1.00 45.99
ATOM   5353  CD  GLU  1227      41.761  17.469  -9.612  1.00 57.33
ATOM   5354  OE1 GLU  1227      42.430  16.824  -8.757  1.00 58.99
ATOM   5355  OE2 GLU  1227      42.320  18.250 -10.424  1.00 62.92
ATOM   5356  C   GLU  1227      38.798  16.542  -6.796  1.00 20.14
```

FIG.23.89

```
ATOM   5357  O   GLU  1227      38.804  17.765  -6.682  1.00 17.51
ATOM   5358  N   CYS  1228      37.855  15.774  -6.269  1.00 16.01
ATOM   5359  CA  CYS  1228      36.805  16.341  -5.452  1.00 20.09
ATOM   5360  C   CYS  1228      37.436  16.918  -4.194  1.00 20.43
ATOM   5361  O   CYS  1228      37.133  18.038  -3.797  1.00 20.36
ATOM   5362  CB  CYS  1228      35.819  15.276  -5.032  1.00 17.24
ATOM   5363  SG  CYS  1228      34.717  15.869  -3.705  1.00 16.56
ATOM   5364  N   VAL  1229      38.321  16.140  -3.578  1.00 18.38
ATOM   5365  CA  VAL  1229      39.012  16.545  -2.355  1.00 18.01
ATOM   5366  CB  VAL  1229      39.862  15.384  -1.726  1.00 10.45
ATOM   5367  CG1 VAL  1229      40.789  15.931  -0.620  1.00 11.88
ATOM   5368  CG2 VAL  1229      38.951  14.329  -1.141  1.00 13.18
ATOM   5369  C   VAL  1229      39.904  17.751  -2.630  1.00 19.38
ATOM   5370  O   VAL  1229      40.005  18.657  -1.795  1.00 18.20
ATOM   5371  N   THR  1230      40.536  17.764  -3.805  1.00 17.44
ATOM   5372  CA  THR  1230      41.401  18.864  -4.201  1.00 17.69
ATOM   5373  CB  THR  1230      42.092  18.554  -5.530  1.00 19.95
ATOM   5374  OG1 THR  1230      43.054  17.510  -5.331  1.00 21.23
ATOM   5375  CG2 THR  1230      42.787  19.782  -6.060  1.00 15.76
ATOM   5376  C   THR  1230      40.606  20.166  -4.290  1.00 15.19
ATOM   5377  O   THR  1230      41.119  21.241  -3.987  1.00 13.68
ATOM   5378  N   ASN  1231      39.332  20.043  -4.638  1.00 12.63
ATOM   5379  CA  ASN  1231      38.438  21.179  -4.733  1.00 17.77
```

FIG.23.90

```
ATOM  5380  CB  ASN 1231      37.264  20.845  -5.649  1.00 19.66
ATOM  5381  CG  ASN 1231      37.690  20.658  -7.063  1.00 22.77
ATOM  5382  OD1 ASN 1231      38.738  21.157  -7.490  1.00 22.53
ATOM  5383  ND2 ASN 1231      36.906  19.909  -7.804  1.00 23.03
ATOM  5384  C   ASN 1231      37.893  21.616  -3.381  1.00 16.56
ATOM  5385  O   ASN 1231      37.706  22.816  -3.144  1.00 16.23
ATOM  5386  N   LEU 1232      37.551  20.648  -2.530  1.00 14.26
ATOM  5387  CA  LEU 1232      37.039  20.932  -1.185  1.00 12.02
ATOM  5388  CB  LEU 1232      36.498  19.659  -0.532  1.00 10.33
ATOM  5389  CG  LEU 1232      35.136  19.256  -1.098  1.00  7.35
ATOM  5390  CD1 LEU 1232      34.702  17.857  -0.664  1.00  6.30
ATOM  5391  CD2 LEU 1232      34.112  20.293  -0.685  1.00  8.09
ATOM  5392  C   LEU 1232      38.140  21.583  -0.354  1.00 10.60
ATOM  5393  O   LEU 1232      37.876  22.440   0.468  1.00 13.90
ATOM  5394  N   GLN 1233      39.381  21.211  -0.619  1.00  9.40
ATOM  5395  CA  GLN 1233      40.527  21.802   0.047  1.00 10.95
ATOM  5396  CB  GLN 1233      41.813  21.154  -0.451  1.00 12.59
ATOM  5397  CG  GLN 1233      43.082  21.692   0.186  1.00 11.94
ATOM  5398  CD  GLN 1233      43.454  20.944   1.459  1.00 20.32
ATOM  5399  OE1 GLN 1233      43.579  19.711   1.456  1.00 14.32
ATOM  5400  NE2 GLN 1233      43.636  21.685   2.554  1.00 14.79
ATOM  5401  C   GLN 1233      40.602  23.299  -0.253  1.00 14.74
ATOM  5402  O   GLN 1233      41.013  24.089   0.600  1.00 18.19
```

FIG.23.91

```
ATOM  5403  N   GLU 1234      40.254  23.687  -1.478  1.00 11.85
ATOM  5404  CA  GLU 1234      40.292  25.103  -1.861  1.00 10.69
ATOM  5405  CB  GLU 1234      40.254  25.266  -3.394  1.00 10.20
ATOM  5406  CG  GLU 1234      40.109  26.712  -3.907  1.00  2.85
ATOM  5407  CD  GLU 1234      41.343  27.573  -3.712  1.00  8.95
ATOM  5408  OE1 GLU 1234      42.384  27.075  -3.232  1.00 18.14
ATOM  5409  OE2 GLU 1234      41.286  28.772  -4.064  1.00 19.71
ATOM  5410  C   GLU 1234      39.113  25.807  -1.200  1.00  6.36
ATOM  5411  O   GLU 1234      39.244  26.914  -0.730  1.00 10.88
ATOM  5412  N   VAL 1235      37.962  25.155  -1.203  1.00  3.91
ATOM  5413  CA  VAL 1235      36.761  25.678  -0.564  1.00  7.66
ATOM  5414  CB  VAL 1235      35.588  24.663  -0.643  1.00  5.62
ATOM  5415  CG1 VAL 1235      34.394  25.122   0.173  1.00  4.56
ATOM  5416  CG2 VAL 1235      35.156  24.485  -2.073  1.00  9.28
ATOM  5417  C   VAL 1235      37.070  25.958   0.911  1.00 14.57
ATOM  5418  O   VAL 1235      36.624  26.970   1.463  1.00 14.73
ATOM  5419  N   ALA 1236      37.823  25.048   1.537  1.00 15.81
ATOM  5420  CA  ALA 1236      38.208  25.167   2.945  1.00 13.64
ATOM  5421  CB  ALA 1236      38.887  23.873   3.445  1.00  6.15
ATOM  5422  C   ALA 1236      39.131  26.369   3.118  1.00 15.64
ATOM  5423  O   ALA 1236      38.976  27.142   4.077  1.00 14.87
ATOM  5424  N   ARG 1237      40.054  26.535   2.165  1.00  9.14
ATOM  5425  CA  ARG 1237      40.984  27.660   2.167  1.00  8.25
```

FIG.23.92

```
ATOM  5426  CB  ARG 1237      42.032  27.507   1.061  1.00  8.87
ATOM  5427  CG  ARG 1237      43.146  28.542   1.170  1.00 11.40
ATOM  5428  CD  ARG 1237      43.929  28.662  -0.128  1.00  5.48
ATOM  5429  NE  ARG 1237      43.041  29.142  -1.171  1.00  9.71
ATOM  5430  CZ  ARG 1237      42.742  30.422  -1.340  1.00 13.92
ATOM  5431 NH1  ARG 1237      43.281  31.332  -0.541  1.00 11.41
ATOM  5432 NH2  ARG 1237      41.859  30.793  -2.258  1.00 15.76
ATOM  5433  C   ARG 1237      40.258  29.014   1.997  1.00  9.36
ATOM  5434  O   ARG 1237      40.513  29.973   2.727  1.00  9.20
ATOM  5435  N   ILE 1238      39.340  29.067   1.049  1.00  7.45
ATOM  5436  CA  ILE 1238      38.591  30.270   0.767  1.00 10.86
ATOM  5437  CB  ILE 1238      37.764  30.092  -0.536  1.00 11.86
ATOM  5438 CG2  ILE 1238      36.747  31.231  -0.685  1.00 11.72
ATOM  5439 CG1  ILE 1238      38.700  29.983  -1.746  1.00  8.57
ATOM  5440 CD1  ILE 1238      37.977  29.666  -3.054  1.00  9.38
ATOM  5441  C   ILE 1238      37.659  30.702   1.908  1.00 11.50
ATOM  5442  O   ILE 1238      37.569  31.891   2.230  1.00 11.72
ATOM  5443  N   VAL 1239      36.951  29.736   2.496  1.00 11.77
ATOM  5444  CA  VAL 1239      36.006  29.989   3.576  1.00  9.26
ATOM  5445  CB  VAL 1239      35.048  28.771   3.746  1.00  6.63
ATOM  5446 CG1  VAL 1239      34.264  28.852   5.020  1.00  8.44
ATOM  5447 CG2  VAL 1239      34.075  28.739   2.602  1.00  5.57
ATOM  5448  C   VAL 1239      36.663  30.388   4.899  1.00 14.36
```

FIG.23.93

```
ATOM   5449  O   VAL  1239      36.249  31.365   5.540  1.00 15.36
ATOM   5450  N   GLY  1240      37.753  29.720   5.263  1.00 14.01
ATOM   5451  CA  GLY  1240      38.368  30.053   6.524  1.00  9.80
ATOM   5452  C   GLY  1240      39.828  30.403   6.608  1.00 13.00
ATOM   5453  O   GLY  1240      40.313  30.636   7.696  1.00 17.82
ATOM   5454  N   ASN  1241      40.554  30.413   5.504  1.00 11.91
ATOM   5455  CA  ASN  1241      41.979  30.736   5.555  1.00 14.24
ATOM   5456  CB  ASN  1241      42.822  29.557   5.082  1.00 19.51
ATOM   5457  CG  ASN  1241      42.800  28.373   6.026  1.00 29.10
ATOM   5458  OD1 ASN  1241      43.763  27.624   6.061  1.00 31.42
ATOM   5459  ND2 ASN  1241      41.675  28.117   6.680  1.00 32.93
ATOM   5460  C   ASN  1241      42.339  31.863   4.623  1.00 16.45
ATOM   5461  O   ASN  1241      43.506  32.027   4.292  1.00 21.90
ATOM   5462  N   SER  1242      41.378  32.658   4.199  1.00 15.33
ATOM   5463  CA  SER  1242      41.734  33.694   3.250  1.00 15.25
ATOM   5464  CB  SER  1242      41.006  33.440   1.934  1.00 15.60
ATOM   5465  OG  SER  1242      39.599  33.389   2.121  1.00 22.94
ATOM   5466  C   SER  1242      41.500  35.116   3.697  1.00 14.71
ATOM   5467  O   SER  1242      41.797  36.057   2.953  1.00 16.28
ATOM   5468  N   GLY  1243      40.960  35.282   4.898  1.00 12.92
ATOM   5469  CA  GLY  1243      40.693  36.616   5.400  1.00  9.53
ATOM   5470  C   GLY  1243      39.217  36.932   5.565  1.00  9.01
ATOM   5471  O   GLY  1243      38.864  38.027   6.002  1.00 11.50
```

FIG.23.94

```
ATOM   5472  N   LEU 1244      38.357  36.003   5.169  1.00  5.30
ATOM   5473  CA  LEU 1244      36.920  36.175   5.315  1.00  5.96
ATOM   5474  CB  LEU 1244      36.152  35.249   4.355  1.00  6.98
ATOM   5475  CG  LEU 1244      35.998  35.540   2.861  1.00  7.31
ATOM   5476  CD1 LEU 1244      35.190  34.413   2.255  1.00  2.00
ATOM   5477  CD2 LEU 1244      35.281  36.871   2.632  1.00  5.17
ATOM   5478  C   LEU 1244      36.562  35.796   6.747  1.00  8.96
ATOM   5479  O   LEU 1244      37.274  35.012   7.372  1.00  7.08
ATOM   5480  N   ASN 1245      35.472  36.351   7.267  1.00  9.02
ATOM   5481  CA  ASN 1245      35.024  36.037   8.612  1.00  6.86
ATOM   5482  CB  ASN 1245      34.405  37.279   9.256  1.00 11.52
ATOM   5483  CG  ASN 1245      34.123  37.101  10.735  1.00  6.02
ATOM   5484  OD1 ASN 1245      33.785  36.020  11.221  1.00  7.40
ATOM   5485  ND2 ASN 1245      34.203  38.195  11.449  1.00  9.26
ATOM   5486  C   ASN 1245      34.007  34.917   8.558  1.00  3.99
ATOM   5487  O   ASN 1245      32.868  35.128   8.209  1.00  8.16
ATOM   5488  N   ILE 1246      34.424  33.722   8.941  1.00  5.99
ATOM   5489  CA  ILE 1246      33.545  32.550   8.927  1.00  7.78
ATOM   5490  CB  ILE 1246      34.368  31.274   9.265  1.00 12.12
ATOM   5491  CG2 ILE 1246      34.591  31.154  10.780  1.00 11.09
ATOM   5492  CG1 ILE 1246      33.671  30.038   8.720  1.00  9.96
ATOM   5493  CD1 ILE 1246      34.515  28.748   8.879  1.00  6.32
ATOM   5494  C   ILE 1246      32.300  32.677   9.824  1.00  6.28
```

FIG.23.95

```
ATOM   5495  O   ILE  1246      31.308  31.963   9.655  1.00 11.95
ATOM   5496  N   TYR  1247      32.326  33.626  10.750  1.00  9.19
ATOM   5497  CA  TYR  1247      31.193  33.857  11.658  1.00 10.80
ATOM   5498  CB  TYR  1247      31.671  34.354  13.035  1.00 12.62
ATOM   5499  CG  TYR  1247      32.213  33.282  13.947  1.00  7.47
ATOM   5500  CD1 TYR  1247      32.224  31.943  13.561  1.00 13.13
ATOM   5501  CE1 TYR  1247      32.712  30.950  14.409  1.00 12.41
ATOM   5502  CD2 TYR  1247      32.699  33.607  15.199  1.00 12.52
ATOM   5503  CE2 TYR  1247      33.174  32.645  16.049  1.00 13.50
ATOM   5504  CZ  TYR  1247      33.183  31.315  15.657  1.00 16.73
ATOM   5505  OH  TYR  1247      33.667  30.366  16.517  1.00 12.14
ATOM   5506  C   TYR  1247      30.195  34.871  11.133  1.00  5.74
ATOM   5507  O   TYR  1247      29.082  34.965  11.648  1.00  6.91
ATOM   5508  N   ASN  1248      30.610  35.650  10.144  1.00  4.94
ATOM   5509  CA  ASN  1248      29.760  36.688   9.584  1.00  7.73
ATOM   5510  CB  ASN  1248      29.731  37.912  10.511  1.00  4.05
ATOM   5511  CG  ASN  1248      28.605  38.880  10.166  1.00  6.16
ATOM   5512  OD1 ASN  1248      28.290  39.109   8.994  1.00 15.77
ATOM   5513  ND2 ASN  1248      27.980  39.434  11.185  1.00  5.24
ATOM   5514  C   ASN  1248      30.410  37.059   8.280  1.00  7.26
ATOM   5515  O   ASN  1248      31.371  37.810   8.269  1.00  4.31
ATOM   5516  N   LEU  1249      29.888  36.509   7.190  1.00 11.85
ATOM   5517  CA  LEU  1249      30.458  36.745   5.859  1.00  9.40
```

FIG.23.96

```
ATOM   5518  CB  LEU 1249      29.570  36.123   4.784  1.00  7.40
ATOM   5519  CG  LEU 1249      30.016  36.277   3.329  1.00  4.43
ATOM   5520  CD1 LEU 1249      31.446  35.883   3.137  1.00  2.00
ATOM   5521  CD2 LEU 1249      29.133  35.405   2.479  1.00  2.74
ATOM   5522  C   LEU 1249      30.660  38.195   5.520  1.00  5.20
ATOM   5523  O   LEU 1249      31.690  38.560   4.965  1.00  7.99
ATOM   5524  N   TYR 1250      29.692  39.006   5.938  1.00  4.98
ATOM   5525  CA  TYR 1250      29.639  40.434   5.674  1.00  5.76
ATOM   5526  CB  TYR 1250      28.182  40.823   5.420  1.00  2.18
ATOM   5527  CG  TYR 1250      27.555  39.939   4.378  1.00  4.32
ATOM   5528  CD1 TYR 1250      26.485  39.096   4.697  1.00  5.22
ATOM   5529  CE1 TYR 1250      25.987  38.174   3.767  1.00  6.53
ATOM   5530  CD2 TYR 1250      28.108  39.862   3.096  1.00  2.53
ATOM   5531  CE2 TYR 1250      27.612  38.962   2.164  1.00  4.06
ATOM   5532  CZ  TYR 1250      26.554  38.117   2.502  1.00  5.21
ATOM   5533  OH  TYR 1250      26.039  37.250   1.550  1.00  6.66
ATOM   5534  C   TYR 1250      30.248  41.368   6.704  1.00  6.45
ATOM   5535  O   TYR 1250      29.915  42.544   6.742  1.00  9.74
ATOM   5536  N   ALA 1251      31.164  40.867   7.513  1.00  4.85
ATOM   5537  CA  ALA 1251      31.809  41.699   8.508  1.00  5.28
ATOM   5538  CB  ALA 1251      31.428  41.228   9.913  1.00  6.54
ATOM   5539  C   ALA 1251      33.299  41.585   8.292  1.00  6.33
ATOM   5540  O   ALA 1251      33.755  40.686   7.600  1.00  7.76
```

FIG.23.97

```
ATOM   5541  N   PRO 1252      34.074  42.555   8.779  1.00  5.83
ATOM   5542  CD  PRO 1252      33.646  43.807   9.421  1.00  3.26
ATOM   5543  CA  PRO 1252      35.529  42.511   8.628  1.00  7.99
ATOM   5544  CB  PRO 1252      35.969  43.880   9.141  1.00 10.32
ATOM   5545  CG  PRO 1252      34.901  44.222  10.123  1.00  7.37
ATOM   5546  C   PRO 1252      36.076  41.412   9.531  1.00 10.99
ATOM   5547  O   PRO 1252      35.388  40.962  10.448  1.00 14.28
ATOM   5548  N   CYS 1253      37.295  40.966   9.275  1.00  6.80
ATOM   5549  CA  CYS 1253      37.889  39.946  10.101  1.00 14.69
ATOM   5550  C   CYS 1253      38.878  40.622  11.006  1.00 16.65
ATOM   5551  O   CYS 1253      39.835  41.225  10.523  1.00 19.87
ATOM   5552  CB  CYS 1253      38.621  38.917   9.257  1.00 13.74
ATOM   5553  SG  CYS 1253      39.432  37.601  10.228  1.00 14.76
ATOM   5554  N   ALA 1254      38.632  40.548  12.311  1.00 21.14
ATOM   5555  CA  ALA 1254      39.535  41.137  13.297  1.00 26.99
ATOM   5556  CB  ALA 1254      38.973  40.974  14.708  1.00 28.81
ATOM   5557  C   ALA 1254      40.897  40.470  13.199  1.00 29.08
ATOM   5558  O   ALA 1254      41.044  39.297  13.538  1.00 29.33
ATOM   5559  N   GLY 1255      41.890  41.243  12.757  1.00 34.01
ATOM   5560  CA  GLY 1255      43.243  40.725  12.592  1.00 35.60
ATOM   5561  C   GLY 1255      43.283  39.675  11.498  1.00 40.58
ATOM   5562  O   GLY 1255      43.736  38.545  11.711  1.00 38.65
ATOM   5563  N   GLY 1256      42.813  40.082  10.319  1.00 45.16
```

FIG.23.98

```
ATOM   5564  CA  GLY  1256      42.728  39.217   9.161  1.00 46.61
ATOM   5565  C   GLY  1256      44.009  38.751   8.513  1.00 47.23
ATOM   5566  O   GLY  1256      44.878  39.528   8.119  1.00 49.78
ATOM   5567  N   VAL  1257      44.070  37.441   8.358  1.00 46.33
ATOM   5568  CA  VAL  1257      45.166  36.739   7.737  1.00 43.27
ATOM   5569  CB  VAL  1257      45.393  35.372   8.440  1.00 45.53
ATOM   5570  CG1 VAL  1257      45.960  35.566   9.829  1.00 42.90
ATOM   5571  CG2 VAL  1257      44.074  34.555   8.447  1.00 45.07
ATOM   5572  C   VAL  1257      44.715  36.379   6.330  1.00 42.32
ATOM   5573  O   VAL  1257      43.853  37.033   5.751  1.00 39.41
ATOM   5574  N   PRO  1258      45.473  35.490   5.701  1.00 43.56
ATOM   5575  CD  PRO  1258      46.844  36.015   5.847  1.00 43.04
ATOM   5576  CA  PRO  1258      45.401  34.849   4.384  1.00 42.07
ATOM   5577  CB  PRO  1258      46.311  35.738   3.519  1.00 41.83
ATOM   5578  CG  PRO  1258      47.013  36.723   4.546  1.00 43.18
ATOM   5579  C   PRO  1258      46.069  33.501   4.673  1.00 40.51
ATOM   5580  O   PRO  1258      46.868  32.988   3.866  1.00 39.55
ATOM   5581  N   SER  1259      45.794  32.972   5.871  1.00 37.33
ATOM   5582  CA  SER  1259      46.406  31.721   6.287  1.00 30.52
ATOM   5583  CB  SER  1259      47.780  32.011   6.875  1.00 28.60
ATOM   5584  OG  SER  1259      48.547  30.830   6.936  1.00 26.07
ATOM   5585  C   SER  1259      45.587  30.930   7.291  1.00 26.46
ATOM   5586  O   SER  1259      44.493  31.340   7.668  1.00 21.66
```

FIG.23.99

ATOM	5610	CB	ARG	1262	47.858	34.922	12.618	1.00	28.18
ATOM	5611	CG	ARG	1262	46.954	34.994	13.822	1.00	26.50
ATOM	5612	CD	ARG	1262	45.915	36.056	13.593	1.00	30.63
ATOM	5613	NE	ARG	1262	44.985	36.203	14.709	1.00	31.92
ATOM	5614	CZ	ARG	1262	45.153	37.050	15.724	1.00	31.48
ATOM	5615	NH1	ARG	1262	46.233	37.831	15.779	1.00	32.38
ATOM	5616	NH2	ARG	1262	44.205	37.149	16.655	1.00	32.05
ATOM	5617	C	ARG	1262	49.690	33.964	13.955	1.00	28.74
ATOM	5618	O	ARG	1262	49.492	33.203	14.903	1.00	29.44
ATOM	5619	N	TYR	1263	50.626	34.898	13.952	1.00	29.68
ATOM	5620	CA	TYR	1263	51.459	35.158	15.118	1.00	31.09
ATOM	5621	CB	TYR	1263	52.936	35.303	14.714	1.00	30.06
ATOM	5622	CG	TYR	1263	53.561	34.069	14.077	1.00	33.51
ATOM	5623	CD1	TYR	1263	53.994	34.094	12.746	1.00	32.99
ATOM	5624	CE1	TYR	1263	54.602	32.978	12.155	1.00	28.92
ATOM	5625	CD2	TYR	1263	53.752	32.891	14.803	1.00	30.89
ATOM	5626	CE2	TYR	1263	54.361	31.772	14.217	1.00	29.84
ATOM	5627	CZ	TYR	1263	54.780	31.833	12.897	1.00	30.19
ATOM	5628	OH	TYR	1263	55.396	30.757	12.333	1.00	29.21
ATOM	5629	C	TYR	1263	50.970	36.447	15.773	1.00	31.03
ATOM	5630	O	TYR	1263	50.470	37.367	15.105	1.00	30.95
ATOM	5631	N	GLU	1264	51.101	36.498	17.087	1.00	31.38
ATOM	5632	CA	GLU	1264	50.697	37.659	17.858	1.00	33.42

FIG.23.101

```
ATOM   5633  CB  GLU  1264      49.425  37.348  18.616  1.00 37.16
ATOM   5634  CG  GLU  1264      48.819  38.532  19.300  1.00 38.61
ATOM   5635  CD  GLU  1264      47.972  38.098  20.447  1.00 40.14
ATOM   5636  OE1 GLU  1264      46.765  38.419  20.435  1.00 37.96
ATOM   5637  OE2 GLU  1264      48.521  37.413  21.344  1.00 40.00
ATOM   5638  C   GLU  1264      51.872  37.839  18.802  1.00 35.26
ATOM   5639  O   GLU  1264      51.917  37.271  19.898  1.00 34.94
ATOM   5640  N   LYS  1265      52.817  38.646  18.335  1.00 39.89
ATOM   5641  CA  LYS  1265      54.079  38.897  19.004  1.00 41.43
ATOM   5642  CB  LYS  1265      53.931  39.220  20.499  1.00 46.86
ATOM   5643  CG  LYS  1265      55.293  39.473  21.147  1.00 54.76
ATOM   5644  CD  LYS  1265      55.199  40.190  22.479  1.00 59.45
ATOM   5645  CE  LYS  1265      56.439  41.053  22.707  1.00 60.55
ATOM   5646  NZ  LYS  1265      57.713  40.287  22.592  1.00 65.22
ATOM   5647  C   LYS  1265      54.809  37.579  18.792  1.00 39.32
ATOM   5648  O   LYS  1265      55.228  37.283  17.667  1.00 39.75
ATOM   5649  N   ASP  1266      54.860  36.740  19.820  1.00 37.46
ATOM   5650  CA  ASP  1266      55.542  35.462  19.700  1.00 32.74
ATOM   5651  CB  ASP  1266      56.882  35.517  20.424  1.00 31.42
ATOM   5652  CG  ASP  1266      57.912  36.369  19.658  1.00 20.00
ATOM   5653  OD1 ASP  1266      57.544  37.044  18.652  1.00 20.00
ATOM   5654  OD2 ASP  1266      59.114  36.349  20.039  1.00 20.00
ATOM   5655  C   ASP  1266      54.701  34.274  20.130  1.00 28.07
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FIG.23.102

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ATOM  5656  O   ASP 1266      55.205  33.261  20.607  1.00 32.14
ATOM  5657  N   THR 1267      53.401  34.438  19.968  1.00 22.25
ATOM  5658  CA  THR 1267      52.437  33.402  20.280  1.00 22.63
ATOM  5659  CB  THR 1267      51.296  33.938  21.194  1.00 19.80
ATOM  5660  OG1 THR 1267      51.811  34.179  22.507  1.00 20.60
ATOM  5661  CG2 THR 1267      50.141  32.939  21.283  1.00 15.20
ATOM  5662  C   THR 1267      51.812  32.965  18.971  1.00 22.93
ATOM  5663  O   THR 1267      51.497  33.798  18.115  1.00 24.18
ATOM  5664  N   VAL 1268      51.705  31.660  18.779  1.00 21.75
ATOM  5665  CA  VAL 1268      51.060  31.164  17.584  1.00 17.51
ATOM  5666  CB  VAL 1268      51.491  29.733  17.234  1.00 18.64
ATOM  5667  CG1 VAL 1268      50.955  29.361  15.842  1.00 18.22
ATOM  5668  CG2 VAL 1268      53.000  29.619  17.285  1.00 17.56
ATOM  5669  C   VAL 1268      49.585  31.146  17.958  1.00 14.97
ATOM  5670  O   VAL 1268      49.216  30.577  18.992  1.00 16.77
ATOM  5671  N   VAL 1269      48.761  31.826  17.166  1.00 14.64
ATOM  5672  CA  VAL 1269      47.342  31.870  17.414  1.00 12.95
ATOM  5673  CB  VAL 1269      46.793  33.307  17.290  1.00  6.85
ATOM  5674  CG1 VAL 1269      45.367  33.343  17.747  1.00  3.93
ATOM  5675  CG2 VAL 1269      47.615  34.264  18.110  1.00  3.36
ATOM  5676  C   VAL 1269      46.666  30.967  16.378  1.00 16.47
ATOM  5677  O   VAL 1269      46.794  31.180  15.166  1.00 15.98
ATOM  5678  N   VAL 1270      45.997  29.929  16.864  1.00 13.62
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FIG.23.103

```
ATOM   5679  CA  VAL  1270      45.289  28.980  16.026  1.00 13.96
ATOM   5680  CB  VAL  1270      45.590  27.555  16.487  1.00  9.13
ATOM   5681  CG1 VAL  1270      44.584  26.581  15.913  1.00 15.74
ATOM   5682  CG2 VAL  1270      46.984  27.186  16.034  1.00  8.89
ATOM   5683  C   VAL  1270      43.808  29.313  16.157  1.00 14.66
ATOM   5684  O   VAL  1270      43.351  29.597  17.264  1.00 17.62
ATOM   5685  N   GLN  1271      43.050  29.286  15.056  1.00 13.61
ATOM   5686  CA  GLN  1271      41.633  29.664  15.125  1.00 11.49
ATOM   5687  CB  GLN  1271      41.466  31.087  14.591  1.00 12.08
ATOM   5688  CG  GLN  1271      42.238  32.063  15.437  1.00 13.81
ATOM   5689  CD  GLN  1271      42.309  33.420  14.848  1.00 16.51
ATOM   5690  OE1 GLN  1271      43.104  33.656  13.949  1.00 23.31
ATOM   5691  NE2 GLN  1271      41.474  34.346  15.344  1.00 11.91
ATOM   5692  C   GLN  1271      40.644  28.720  14.482  1.00 11.75
ATOM   5693  O   GLN  1271      39.492  29.087  14.202  1.00 14.11
ATOM   5694  N   ASP  1272      41.088  27.474  14.342  1.00 14.05
ATOM   5695  CA  ASP  1272      40.301  26.398  13.761  1.00 10.19
ATOM   5696  CB  ASP  1272      41.181  25.589  12.799  1.00 14.03
ATOM   5697  CG  ASP  1272      40.444  24.412  12.154  1.00 13.51
ATOM   5698  OD1 ASP  1272      39.203  24.305  12.256  1.00 20.46
ATOM   5699  OD2 ASP  1272      41.126  23.571  11.541  1.00 24.72
ATOM   5700  C   ASP  1272      39.875  25.535  14.923  1.00  9.82
ATOM   5701  O   ASP  1272      40.695  24.843  15.483  1.00 12.05
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FIG.23.104

```
ATOM   5702  N   LEU 1273      38.588  25.543  15.242  1.00  6.07
ATOM   5703  CA  LEU 1273      38.058  24.790  16.365  1.00 10.92
ATOM   5704  CB  LEU 1273      36.845  25.509  16.951  1.00  5.16
ATOM   5705  CG  LEU 1273      37.019  26.976  17.328  1.00  6.05
ATOM   5706  CD1 LEU 1273      35.755  27.440  18.001  1.00  4.65
ATOM   5707  CD2 LEU 1273      38.181  27.165  18.226  1.00  7.00
ATOM   5708  C   LEU 1273      37.748  23.319  16.088  1.00 13.09
ATOM   5709  O   LEU 1273      37.129  22.636  16.922  1.00 10.63
ATOM   5710  N   GLY 1274      38.196  22.876  14.903  1.00 13.95
ATOM   5711  CA  GLY 1274      38.070  21.504  14.414  1.00 12.07
ATOM   5712  C   GLY 1274      36.725  20.852  14.204  1.00 12.36
ATOM   5713  O   GLY 1274      36.622  19.632  14.336  1.00 13.37
ATOM   5714  N   ASN 1275      35.708  21.618  13.823  1.00  9.66
ATOM   5715  CA  ASN 1275      34.383  21.034  13.644  1.00  9.00
ATOM   5716  CB  ASN 1275      33.334  21.832  14.429  1.00 11.33
ATOM   5717  CG  ASN 1275      33.670  21.963  15.895  1.00 15.82
ATOM   5718  OD1 ASN 1275      33.934  20.977  16.579  1.00 17.09
ATOM   5719  ND2 ASN 1275      33.675  23.191  16.387  1.00 10.47
ATOM   5720  C   ASN 1275      33.906  20.941  12.201  1.00  9.66
ATOM   5721  O   ASN 1275      32.873  20.343  11.927  1.00  9.68
ATOM   5722  N   ILE 1276      34.691  21.489  11.286  1.00  9.97
ATOM   5723  CA  ILE 1276      34.307  21.568   9.877  1.00 11.82
ATOM   5724  CB  ILE 1276      34.343  23.084   9.423  1.00 11.44
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FIG.23.105

```
ATOM   5725  CG2 ILE  1276      34.040  23.248   7.951  1.00 10.15
ATOM   5726  CG1 ILE  1276      33.346  23.886  10.264  1.00  9.40
ATOM   5727  CD1 ILE  1276      33.562  25.376  10.229  1.00  2.81
ATOM   5728  C   ILE  1276      35.232  20.737   9.001  1.00  9.96
ATOM   5729  O   ILE  1276      36.454  20.768   9.192  1.00  7.64
ATOM   5730  N   PHE  1277      34.633  19.971   8.077  1.00 14.17
ATOM   5731  CA  PHE  1277      35.362  19.109   7.122  1.00 13.77
ATOM   5732  CB  PHE  1277      36.213  19.970   6.145  1.00 11.84
ATOM   5733  CG  PHE  1277      35.386  20.878   5.232  1.00 13.15
ATOM   5734  CD1 PHE  1277      35.796  22.188   4.963  1.00 12.93
ATOM   5735  CD2 PHE  1277      34.203  20.419   4.640  1.00 14.08
ATOM   5736  CE1 PHE  1277      35.043  23.027   4.113  1.00 13.33
ATOM   5737  CE2 PHE  1277      33.449  21.252   3.792  1.00  9.73
ATOM   5738  CZ  PHE  1277      33.879  22.559   3.530  1.00 12.32
ATOM   5739  C   PHE  1277      36.236  18.076   7.843  1.00 11.52
ATOM   5740  O   PHE  1277      37.285  17.660   7.340  1.00 10.20
ATOM   5741  N   THR  1278      35.768  17.624   9.003  1.00 11.71
ATOM   5742  CA  THR  1278      36.526  16.653   9.807  1.00 14.47
ATOM   5743  CB  THR  1278      35.859  16.413  11.188  1.00 12.43
ATOM   5744  OG1 THR  1278      34.504  15.983  10.997  1.00  5.40
ATOM   5745  CG2 THR  1278      35.858  17.670  12.011  1.00 14.30
ATOM   5746  C   THR  1278      36.702  15.289   9.129  1.00 16.87
ATOM   5747  O   THR  1278      37.726  14.624   9.333  1.00 21.05
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FIG.23.106

```
ATOM   5748  N   ARG  1279      35.709  14.896   8.326  1.00 14.96
ATOM   5749  CA  ARG  1279      35.703  13.614   7.631  1.00 15.72
ATOM   5750  CB  ARG  1279      34.276  13.103   7.475  1.00 10.95
ATOM   5751  CG  ARG  1279      33.664  12.659   8.766  1.00 17.88
ATOM   5752  CD  ARG  1279      34.529  11.595   9.377  1.00 17.45
ATOM   5753  NE  ARG  1279      34.157  11.334  10.757  1.00 25.93
ATOM   5754  CZ  ARG  1279      34.196  10.135  11.327  1.00 31.46
ATOM   5755  NH1 ARG  1279      34.587   9.072  10.631  1.00 34.18
ATOM   5756  NH2 ARG  1279      33.875  10.000  12.605  1.00 35.30
ATOM   5757  C   ARG  1279      36.362  13.607   6.275  1.00 15.10
ATOM   5758  O   ARG  1279      36.410  12.563   5.623  1.00 17.91
ATOM   5759  N   LEU  1280      36.900  14.746   5.863  1.00 14.43
ATOM   5760  CA  LEU  1280      37.543  14.846   4.574  1.00 12.87
ATOM   5761  CB  LEU  1280      37.341  16.230   3.937  1.00 12.66
ATOM   5762  CG  LEU  1280      35.919  16.555   3.482  1.00 11.37
ATOM   5763  CD1 LEU  1280      35.851  17.965   2.842  1.00 12.24
ATOM   5764  CD2 LEU  1280      35.456  15.453   2.519  1.00 10.36
ATOM   5765  C   LEU  1280      38.993  14.615   4.736  1.00 12.38
ATOM   5766  O   LEU  1280      39.582  15.120   5.671  1.00 11.84
ATOM   5767  N   PRO  1281      39.603  13.847   3.815  1.00 13.92
ATOM   5768  CD  PRO  1281      38.987  13.063   2.725  1.00  9.83
ATOM   5769  CA  PRO  1281      41.037  13.588   3.913  1.00 14.25
ATOM   5770  CB  PRO  1281      41.240  12.413   2.960  1.00 15.39
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FIG.23.107

```
ATOM   5771  CG  PRO  1281      40.184  12.630   1.920  1.00 12.69
ATOM   5772  C   PRO  1281      41.828  14.813   3.468  1.00 17.51
ATOM   5773  O   PRO  1281      42.659  14.718   2.569  1.00 21.78
ATOM   5774  N   LEU  1282      41.589  15.952   4.115  1.00 16.38
ATOM   5775  CA  LEU  1282      42.273  17.185   3.769  1.00 13.89
ATOM   5776  CB  LEU  1282      41.417  18.390   4.201  1.00 15.96
ATOM   5777  CG  LEU  1282      40.001  18.593   3.637  1.00 15.64
ATOM   5778  CD1 LEU  1282      39.424  19.886   4.192  1.00  9.38
ATOM   5779  CD2 LEU  1282      39.973  18.602   2.108  1.00 11.12
ATOM   5780  C   LEU  1282      43.689  17.315   4.354  1.00 15.19
ATOM   5781  O   LEU  1282      44.111  16.514   5.177  1.00 18.07
ATOM   5782  N   LYS  1283      44.466  18.252   3.828  1.00 15.73
ATOM   5783  CA  LYS  1283      45.795  18.500   4.355  1.00 15.07
ATOM   5784  CB  LYS  1283      46.727  18.996   3.272  1.00 14.37
ATOM   5785  CG  LYS  1283      46.940  18.014   2.179  1.00 19.99
ATOM   5786  CD  LYS  1283      48.122  18.437   1.340  1.00 24.07
ATOM   5787  CE  LYS  1283      47.688  18.943  -0.014  1.00 30.06
ATOM   5788  NZ  LYS  1283      48.865  19.337  -0.841  1.00 36.72
ATOM   5789  C   LYS  1283      45.564  19.601   5.369  1.00 17.48
ATOM   5790  O   LYS  1283      44.858  20.563   5.078  1.00 19.13
ATOM   5791  N   ARG  1284      46.140  19.456   6.555  1.00 17.51
ATOM   5792  CA  ARG  1284      45.957  20.418   7.630  1.00 15.14
ATOM   5793  CB  ARG  1284      44.941  19.890   8.652  1.00 12.29
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FIG.23.108

```
ATOM   5794  CG  ARG  1284      43.569  19.576   8.085  1.00 16.09
ATOM   5795  CD  ARG  1284      42.703  18.923   9.135  1.00 20.20
ATOM   5796  NE  ARG  1284      41.326  18.588   8.722  1.00 21.27
ATOM   5797  CZ  ARG  1284      40.964  17.444   8.139  1.00 10.43
ATOM   5798  NH1 ARG  1284      41.871  16.526   7.861  1.00 16.46
ATOM   5799  NH2 ARG  1284      39.676  17.160   7.958  1.00  9.96
ATOM   5800  C   ARG  1284      47.268  20.678   8.327  1.00 17.27
ATOM   5801  O   ARG  1284      48.242  19.978   8.112  1.00 21.46
ATOM   5802  N   MET  1285      47.290  21.750   9.108  1.00 19.19
ATOM   5803  CA  MET  1285      48.455  22.173   9.878  1.00 19.83
ATOM   5804  CB  MET  1285      48.135  23.511  10.579  1.00 18.32
ATOM   5805  CG  MET  1285      49.320  24.226  11.260  1.00 21.37
ATOM   5806  SD  MET  1285      48.808  25.697  12.236  1.00 18.33
ATOM   5807  CE  MET  1285      50.344  26.231  12.870  1.00 15.58
ATOM   5808  C   MET  1285      48.713  21.115  10.935  1.00 19.93
ATOM   5809  O   MET  1285      47.775  20.540  11.477  1.00 16.24
ATOM   5810  N   TRP  1286      49.974  20.897  11.272  1.00 19.54
ATOM   5811  CA  TRP  1286      50.304  19.919  12.296  1.00 18.41
ATOM   5812  CB  TRP  1286      51.751  19.501  12.137  1.00 18.01
ATOM   5813  CG  TRP  1286      52.088  18.229  12.802  1.00 20.70
ATOM   5814  CD2 TRP  1286      53.376  17.622  12.842  1.00 18.84
ATOM   5815  CE2 TRP  1286      53.266  16.443  13.612  1.00 20.91
ATOM   5816  CE3 TRP  1286      54.620  17.969  12.309  1.00 21.23
```

FIG.23.109

```
ATOM   5817  CD1 TRP  1286      51.253  17.411  13.519  1.00 18.64
ATOM   5818  NE1 TRP  1286      51.958  16.335  14.012  1.00 19.87
ATOM   5819  CZ2 TRP  1286      54.355  15.608  13.864  1.00 19.80
ATOM   5820  CZ3 TRP  1286      55.704  17.140  12.556  1.00 22.59
ATOM   5821  CH2 TRP  1286      55.564  15.971  13.328  1.00 16.66
ATOM   5822  C   TRP  1286      50.060  20.480  13.712  1.00 14.95
ATOM   5823  O   TRP  1286      50.987  20.798  14.436  1.00 15.10
ATOM   5824  N   HIS  1287      48.804  20.624  14.098  1.00 15.33
ATOM   5825  CA  HIS  1287      48.490  21.142  15.414  1.00 19.07
ATOM   5826  CB  HIS  1287      46.985  21.144  15.631  1.00 23.63
ATOM   5827  CG  HIS  1287      46.268  22.191  14.836  1.00 34.57
ATOM   5828  CD2 HIS  1287      45.328  22.091  13.864  1.00 35.23
ATOM   5829  ND1 HIS  1287      46.497  23.538  15.009  1.00 41.86
ATOM   5830  CE1 HIS  1287      45.731  24.225  14.181  1.00 43.57
ATOM   5831  NE2 HIS  1287      45.011  23.373  13.474  1.00 40.64
ATOM   5832  C   HIS  1287      49.167  20.309  16.486  1.00 19.76
ATOM   5833  O   HIS  1287      49.543  20.821  17.543  1.00 20.50
ATOM   5834  N   GLN  1288      49.377  19.038  16.178  1.00 21.58
ATOM   5835  CA  GLN  1288      50.009  18.107  17.105  1.00 25.74
ATOM   5836  CB  GLN  1288      49.775  16.676  16.633  1.00 27.82
ATOM   5837  CG  GLN  1288      48.325  16.204  16.796  1.00 34.64
ATOM   5838  CD  GLN  1288      47.846  16.193  18.252  1.00 39.87
ATOM   5839  OE1 GLN  1288      48.655  16.199  19.191  1.00 43.32
```

FIG.23.110

ATOM	5840	NE2	GLN	1288	46.525	16.183	18.444	1.00	40.01
ATOM	5841	C	GLN	1288	51.486	18.330	17.444	1.00	22.73
ATOM	5842	O	GLN	1288	51.970	17.815	18.456	1.00	30.74
ATOM	5881	N	GLY	1294	57.449	24.162	21.880	1.00	18.00
ATOM	5882	CA	GLY	1294	57.755	25.015	23.003	1.00	20.64
ATOM	5883	C	GLY	1294	57.397	26.468	22.759	1.00	21.76
ATOM	5884	O	GLY	1294	57.763	27.334	23.533	1.00	26.39
ATOM	5885	N	ASP	1295	56.725	26.763	21.662	1.00	21.95
ATOM	5886	CA	ASP	1295	56.340	28.140	21.397	1.00	17.91
ATOM	5887	CB	ASP	1295	56.141	28.370	19.893	1.00	19.96
ATOM	5888	CG	ASP	1295	57.432	28.231	19.101	1.00	15.94
ATOM	5889	OD1	ASP	1295	58.516	28.560	19.635	1.00	20.10
ATOM	5890	OD2	ASP	1295	57.351	27.806	17.925	1.00	16.30
ATOM	5891	C	ASP	1295	55.024	28.318	22.131	1.00	16.27
ATOM	5892	O	ASP	1295	54.368	27.329	22.447	1.00	14.67
ATOM	5893	N	LYS	1296	54.688	29.559	22.477	1.00	17.87
ATOM	5894	CA	LYS	1296	53.430	29.813	23.158	1.00	16.64
ATOM	5895	CB	LYS	1296	53.398	31.198	23.776	1.00	26.01
ATOM	5896	CG	LYS	1296	54.282	31.364	24.980	1.00	34.95
ATOM	5897	CD	LYS	1296	54.176	32.788	25.508	1.00	44.36
ATOM	5898	CE	LYS	1296	55.558	33.376	25.784	1.00	49.30

FIG.23.111

```
ATOM   5899  NZ  LYS  1296      55.429  34.748  26.355  1.00 54.50
ATOM   5900  C   LYS  1296      52.360  29.724  22.101  1.00 16.29
ATOM   5901  O   LYS  1296      52.506  30.290  21.033  1.00 19.55
ATOM   5902  N   VAL  1297      51.277  29.031  22.422  1.00 19.34
ATOM   5903  CA  VAL  1297      50.165  28.810  21.510  1.00 15.33
ATOM   5904  CB  VAL  1297      49.976  27.286  21.215  1.00 13.90
ATOM   5905  CG1 VAL  1297      48.886  27.074  20.194  1.00 14.41
ATOM   5906  CG2 VAL  1297      51.248  26.667  20.747  1.00 10.04
ATOM   5907  C   VAL  1297      48.893  29.220  22.205  1.00 16.04
ATOM   5908  O   VAL  1297      48.723  28.923  23.393  1.00 19.62
ATOM   5909  N   ARG  1298      47.992  29.884  21.488  1.00 13.63
ATOM   5910  CA  ARG  1298      46.702  30.226  22.058  1.00 12.09
ATOM   5911  CB  ARG  1298      46.644  31.682  22.542  1.00 13.21
ATOM   5912  CG  ARG  1298      45.383  32.000  23.375  1.00 12.25
ATOM   5913  CD  ARG  1298      45.290  33.470  23.767  1.00 11.33
ATOM   5914  NE  ARG  1298      45.056  34.375  22.638  1.00 14.42
ATOM   5915  CZ  ARG  1298      45.973  35.176  22.102  1.00 13.34
ATOM   5916  NH1 ARG  1298      47.211  35.197  22.572  1.00 16.58
ATOM   5917  NH2 ARG  1298      45.647  35.971  21.090  1.00 12.19
ATOM   5918  C   ARG  1298      45.653  30.000  20.983  1.00 12.37
ATOM   5919  O   ARG  1298      45.919  30.200  19.806  1.00 15.30
ATOM   5920  N   MET  1299      44.489  29.506  21.366  1.00 12.41
ATOM   5921  CA  MET  1299      43.424  29.337  20.399  1.00 10.79
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FIG:23.112

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ATOM  5922  CB  MET 1299      42.731  27.980  20.524  1.00 13.84
ATOM  5923  CG  MET 1299      41.467  27.880  19.674  1.00 17.13
ATOM  5924  SD  MET 1299      40.885  26.225  19.406  1.00 19.68
ATOM  5925  CE  MET 1299      42.161  25.698  18.296  1.00 12.26
ATOM  5926  C   MET 1299      42.410  30.465  20.628  1.00 13.87
ATOM  5927  O   MET 1299      41.961  30.672  21.763  1.00  8.96
ATOM  5928  N   ASP 1300      42.058  31.175  19.555  1.00 13.31
ATOM  5929  CA  ASP 1300      41.093  32.264  19.610  1.00  9.27
ATOM  5930  CB  ASP 1300      41.693  33.558  19.066  1.00 14.09
ATOM  5931  CG  ASP 1300      42.500  34.328  20.094  1.00 14.70
ATOM  5932  OD1 ASP 1300      42.633  33.857  21.247  1.00 16.06
ATOM  5933  OD2 ASP 1300      43.009  35.408  19.737  1.00 20.44
ATOM  5934  C   ASP 1300      40.004  31.869  18.664  1.00  9.11
ATOM  5935  O   ASP 1300      40.231  31.083  17.760  1.00 11.34
ATOM  5936  N   PRO 1301      38.785  32.351  18.893  1.00  8.10
ATOM  5937  CD  PRO 1301      38.272  33.182  20.009  1.00  7.47
ATOM  5938  CA  PRO 1301      37.722  31.986  17.952  1.00  9.45
ATOM  5939  CB  PRO 1301      36.466  32.613  18.576  1.00 10.94
ATOM  5940  CG  PRO 1301      36.843  32.747  20.087  1.00  6.66
ATOM  5941  C   PRO 1301      38.155  32.711  16.645  1.00 10.72
ATOM  5942  O   PRO 1301      38.889  33.706  16.710  1.00 10.77
ATOM  5943  N   PRO 1302      37.772  32.197  15.456  1.00  7.99
ATOM  5944  CD  PRO 1302      36.830  31.085  15.219  1.00  7.42
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FIG.23.113

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ATOM   5945  CA  PRO  1302      38.139  32.812  14.183  1.00   9.36
ATOM   5946  CB  PRO  1302      37.499  31.878  13.176  1.00   9.92
ATOM   5947  CG  PRO  1302      36.256  31.446  13.890  1.00   6.38
ATOM   5948  C   PRO  1302      37.643  34.239  13.992  1.00   9.95
ATOM   5949  O   PRO  1302      36.445  34.499  14.117  1.00  13.82
ATOM   5950  N   CYS  1303      38.572  35.135  13.632  1.00  10.17
ATOM   5951  CA  CYS  1303      38.294  36.560  13.377  1.00  12.34
ATOM   5952  C   CYS  1303      37.784  37.291  14.580  1.00  11.83
ATOM   5953  O   CYS  1303      37.115  38.310  14.441  1.00  13.71
ATOM   5954  CB  CYS  1303      37.300  36.755  12.230  1.00  13.09
ATOM   5955  SG  CYS  1303      37.950  36.288  10.602  1.00  13.66
ATOM   5956  N   THR  1304      38.157  36.805  15.753  1.00  17.57
ATOM   5957  CA  THR  1304      37.708  37.374  17.005  1.00  18.74
ATOM   5958  CB  THR  1304      37.017  36.290  17.837  1.00  17.56
ATOM   5959  OG1 THR  1304      35.804  35.898  17.191  1.00  23.25
ATOM   5960  CG2 THR  1304      36.732  36.772  19.249  1.00  23.07
ATOM   5961  C   THR  1304      38.861  37.927  17.815  1.00  19.28
ATOM   5962  O   THR  1304      39.858  37.235  18.047  1.00  22.66
ATOM   5963  N   ASN  1305      38.692  39.168  18.266  1.00  22.15
ATOM   5964  CA  ASN  1305      39.685  39.859  19.086  1.00  24.22
ATOM   5965  CB  ASN  1305      39.723  41.336  18.729  1.00  27.21
ATOM   5966  CG  ASN  1305      40.682  42.119  19.595  1.00  24.55
ATOM   5967  OD1 ASN  1305      41.494  41.564  20.318  1.00  22.42
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FIG.23.114

```
ATOM   5968  ND2 ASN 1305      40.569  43.441  19.484  1.00 28.27
ATOM   5969  C   ASN 1305      39.251  39.670  20.542  1.00 24.27
ATOM   5970  O   ASN 1305      38.320  40.315  21.025  1.00 26.32
ATOM   5971  N   THR 1306      39.936  38.763  21.228  1.00 22.99
ATOM   5972  CA  THR 1306      39.639  38.432  22.609  1.00 20.50
ATOM   5973  CB  THR 1306      40.133  37.008  22.905  1.00 15.82
ATOM   5974  OG1 THR 1306      41.505  36.902  22.529  1.00 17.57
ATOM   5975  CG2 THR 1306      39.344  36.005  22.102  1.00 17.16
ATOM   5976  C   THR 1306      40.214  39.387  23.651  1.00 17.53
ATOM   5977  O   THR 1306      39.942  39.223  24.842  1.00 15.35
ATOM   5978  N   THR 1307      40.958  40.396  23.201  1.00 14.79
ATOM   5979  CA  THR 1307      41.599  41.363  24.090  1.00 19.15
ATOM   5980  CB  THR 1307      42.352  42.433  23.298  1.00 21.40
ATOM   5981  OG1 THR 1307      43.348  41.795  22.489  1.00 26.67
ATOM   5982  CG2 THR 1307      43.048  43.422  24.247  1.00 25.86
ATOM   5983  C   THR 1307      40.735  42.039  25.157  1.00 16.30
ATOM   5984  O   THR 1307      41.047  41.948  26.333  1.00 17.06
ATOM   5985  N   ALA 1308      39.696  42.755  24.760  1.00 15.01
ATOM   5986  CA  ALA 1308      38.834  43.404  25.722  1.00 14.41
ATOM   5987  CB  ALA 1308      37.578  43.908  25.028  1.00 14.08
ATOM   5988  C   ALA 1308      38.471  42.454  26.885  1.00 18.25
ATOM   5989  O   ALA 1308      38.829  42.715  28.033  1.00 21.28
ATOM   5990  N   ALA 1309      37.823  41.331  26.569  1.00 17.96
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FIG.23.115

ATOM	5991	CA	ALA	1309	37.411	40.331	27.560	1.00	14.58
ATOM	5992	CB	ALA	1309	36.617	39.239	26.895	1.00	10.46
ATOM	5993	C	ALA	1309	38.546	39.724	28.393	1.00	15.70
ATOM	5994	O	ALA	1309	38.443	39.633	29.617	1.00	17.76
ATOM	5995	N	SER	1310	39.631	39.336	27.745	1.00	10.89
ATOM	5996	CA	SER	1310	40.756	38.751	28.431	1.00	11.22
ATOM	5997	CB	SER	1310	41.742	38.236	27.420	1.00	6.17
ATOM	5998	OG	SER	1310	42.884	37.677	28.040	1.00	14.61
ATOM	5999	C	SER	1310	41.414	39.768	29.328	1.00	20.38
ATOM	6000	O	SER	1310	41.874	39.437	30.427	1.00	21.24
ATOM	6131	N	GLN	1327	45.603	30.761	42.510	1.00	24.88
ATOM	6132	CA	GLN	1327	46.475	29.782	41.879	1.00	26.79
ATOM	6133	CB	GLN	1327	46.504	28.485	42.705	1.00	31.85
ATOM	6134	CG	GLN	1327	45.367	27.496	42.400	1.00	37.11
ATOM	6135	CD	GLN	1327	44.321	27.415	43.501	1.00	45.27
ATOM	6136	OE1	GLN	1327	44.203	28.338	44.325	1.00	51.95
ATOM	6137	NE2	GLN	1327	43.534	26.318	43.508	1.00	41.15
ATOM	6138	C	GLN	1327	46.093	29.478	40.422	1.00	24.68
ATOM	6139	O	GLN	1327	46.959	29.135	39.622	1.00	27.37
ATOM	6140	N	LEU	1328	44.808	29.566	40.085	1.00	20.03
ATOM	6141	CA	LEU	1328	44.366	29.289	38.724	1.00	16.82
ATOM	6142	CB	LEU	1328	42.876	29.581	38.577	1.00	14.85

FIG.23.116

```
ATOM   6143  CG  LEU  1328      41.969  28.731  39.456  1.00 17.98
ATOM   6144  CD1 LEU  1328      40.534  29.008  39.110  1.00 14.73
ATOM   6145  CD2 LEU  1328      42.280  27.256  39.267  1.00 19.60
ATOM   6146  C   LEU  1328      45.159  30.122  37.723  1.00 17.22
ATOM   6147  O   LEU  1328      45.492  31.278  38.004  1.00 18.76
ATOM   6148  N   PRO  1329      45.531  29.532  36.562  1.00 16.86
ATOM   6149  CD  PRO  1329      45.201  28.176  36.074  1.00 17.84
ATOM   6150  CA  PRO  1329      46.296  30.268  35.547  1.00 15.49
ATOM   6151  CB  PRO  1329      46.741  29.165  34.599  1.00 17.24
ATOM   6152  CG  PRO  1329      45.570  28.247  34.616  1.00 13.96
ATOM   6153  C   PRO  1329      45.391  31.276  34.854  1.00 17.40
ATOM   6154  O   PRO  1329      44.161  31.281  35.074  1.00 18.71
ATOM   6155  N   GLN  1330      45.997  32.122  34.021  1.00 21.18
ATOM   6156  CA  GLN  1330      45.253  33.162  33.319  1.00 22.07
ATOM   6157  CB  GLN  1330      46.171  34.056  32.499  1.00 24.05
ATOM   6158  CG  GLN  1330      46.602  33.452  31.198  1.00 35.03
ATOM   6159  CD  GLN  1330      47.345  34.440  30.341  1.00 36.38
ATOM   6160  OE1 GLN  1330      46.902  34.768  29.247  1.00 37.43
ATOM   6161  NE2 GLN  1330      48.493  34.912  30.827  1.00 41.64
ATOM   6162  C   GLN  1330      44.137  32.663  32.444  1.00 20.80
ATOM   6163  O   GLN  1330      44.210  31.580  31.864  1.00 20.17
ATOM   6164  N   TRP  1331      43.114  33.500  32.355  1.00 19.19
ATOM   6165  CA  TRP  1331      41.917  33.259  31.582  1.00 15.74
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FIG:23.117

```
ATOM   6166  CB  TRP  1331      40.811  34.209  32.086  1.00  9.68
ATOM   6167  CG  TRP  1331      39.433  33.939  31.543  1.00  7.90
ATOM   6168  CD2 TRP  1331      38.861  34.476  30.337  1.00  9.80
ATOM   6169  CE2 TRP  1331      37.568  33.927  30.207  1.00 10.42
ATOM   6170  CE3 TRP  1331      39.322  35.370  29.346  1.00 12.32
ATOM   6171  CD1 TRP  1331      38.490  33.117  32.079  1.00  8.51
ATOM   6172  NE1 TRP  1331      37.366  33.107  31.290  1.00  5.81
ATOM   6173  CZ2 TRP  1331      36.713  34.239  29.124  1.00 11.58
ATOM   6174  CZ3 TRP  1331      38.474  35.681  28.265  1.00  4.60
ATOM   6175  CH2 TRP  1331      37.185  35.114  28.171  1.00  7.15
ATOM   6176  C   TRP  1331      42.179  33.537  30.100  1.00 17.56
ATOM   6177  O   TRP  1331      42.880  34.495  29.752  1.00 16.46
ATOM   6178  N   ASP  1332      41.675  32.644  29.248  1.00 17.58
ATOM   6179  CA  ASP  1332      41.743  32.767  27.791  1.00 15.86
ATOM   6180  CB  ASP  1332      42.677  31.745  27.134  1.00 15.21
ATOM   6181  CG  ASP  1332      44.105  31.867  27.590  1.00 14.99
ATOM   6182  OD1 ASP  1332      44.740  32.912  27.336  1.00 17.52
ATOM   6183  OD2 ASP  1332      44.607  30.878  28.182  1.00 24.22
ATOM   6184  C   ASP  1332      40.323  32.399  27.419  1.00 13.51
ATOM   6185  O   ASP  1332      39.692  31.615  28.142  1.00 13.41
ATOM   6186  N   MET  1333      39.813  32.955  26.319  1.00 13.87
ATOM   6187  CA  MET  1333      38.451  32.644  25.885  1.00 11.98
ATOM   6188  CB  MET  1333      37.995  33.568  24.754  1.00 14.30
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FIG.23.118

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ATOM   6189  CG  MET  1333      36.467  33.720  24.669  1.00 15.28
ATOM   6190  SD  MET  1333      36.010  34.950  23.447  1.00 32.07
ATOM   6191  CE  MET  1333      36.098  36.463  24.442  1.00 17.03
ATOM   6192  C   MET  1333      38.296  31.179  25.477  1.00  7.62
ATOM   6193  O   MET  1333      37.257  30.557  25.735  1.00 10.01
ATOM   6194  N   CYS  1334      39.347  30.607  24.903  1.00 10.15
ATOM   6195  CA  CYS  1334      39.318  29.205  24.494  1.00 12.87
ATOM   6196  C   CYS  1334      40.586  28.551  24.978  1.00 10.05
ATOM   6197  O   CYS  1334      41.649  29.202  25.012  1.00 11.91
ATOM   6198  CB  CYS  1334      39.277  29.041  22.948  1.00 12.65
ATOM   6199  SG  CYS  1334      37.837  29.735  22.072  1.00 13.22
ATOM   6200  N   ASN  1335      40.489  27.277  25.368  1.00 12.61
ATOM   6201  CA  ASN  1335      41.688  26.550  25.763  1.00 11.39
ATOM   6202  CB  ASN  1335      41.482  25.711  27.021  1.00 11.86
ATOM   6203  CG  ASN  1335      42.794  25.159  27.535  1.00 11.49
ATOM   6204  OD1 ASN  1335      43.336  24.212  26.981  1.00 21.62
ATOM   6205  ND2 ASN  1335      43.373  25.832  28.514  1.00 23.00
ATOM   6206  C   ASN  1335      42.165  25.646  24.606  1.00  8.19
ATOM   6207  O   ASN  1335      41.466  24.711  24.199  1.00  9.72
ATOM   6208  N   PHE  1336      43.339  25.948  24.065  1.00 11.32
ATOM   6209  CA  PHE  1336      43.903  25.174  22.968  1.00 13.29
ATOM   6210  CB  PHE  1336      45.292  25.693  22.614  1.00 11.35
ATOM   6211  CG  PHE  1336      46.031  24.822  21.627  1.00 20.08
```

FIG.23.119

```
ATOM   6212  CD1 PHE 1336      45.544  24.630  20.332  1.00 18.83
ATOM   6213  CD2 PHE 1336      47.227  24.190  21.993  1.00 15.81
ATOM   6214  CE1 PHE 1336      46.241  23.820  19.418  1.00 18.03
ATOM   6215  CE2 PHE 1336      47.924  23.381  21.087  1.00 18.32
ATOM   6216  CZ  PHE 1336      47.432  23.198  19.802  1.00 15.81
ATOM   6217  C   PHE 1336      43.959  23.682  23.289  1.00 13.67
ATOM   6218  O   PHE 1336      43.398  22.872  22.569  1.00 15.69
ATOM   6219  N   LEU 1337      44.643  23.328  24.371  1.00 16.29
ATOM   6220  CA  LEU 1337      44.772  21.939  24.786  1.00 14.49
ATOM   6221  CB  LEU 1337      45.577  21.864  26.066  1.00 18.32
ATOM   6222  CG  LEU 1337      46.992  21.442  25.697  1.00 24.74
ATOM   6223  CD1 LEU 1337      48.008  22.158  26.525  1.00 29.97
ATOM   6224  CD2 LEU 1337      47.123  19.932  25.829  1.00 27.19
ATOM   6225  C   LEU 1337      43.464  21.187  24.937  1.00 14.74
ATOM   6226  O   LEU 1337      43.357  20.025  24.525  1.00 16.63
ATOM   6227  N   VAL 1338      42.461  21.839  25.517  1.00 10.36
ATOM   6228  CA  VAL 1338      41.158  21.206  25.676  1.00 10.04
ATOM   6229  CB  VAL 1338      40.137  22.110  26.402  1.00  8.16
ATOM   6230  CG1 VAL 1338      38.744  21.478  26.320  1.00 10.40
ATOM   6231  CG2 VAL 1338      40.523  22.294  27.868  1.00 12.50
ATOM   6232  C   VAL 1338      40.582  20.852  24.308  1.00 14.79
ATOM   6233  O   VAL 1338      40.089  19.745  24.102  1.00 15.49
ATOM   6234  N   ASN 1339      40.612  21.823  23.394  1.00 18.63
```

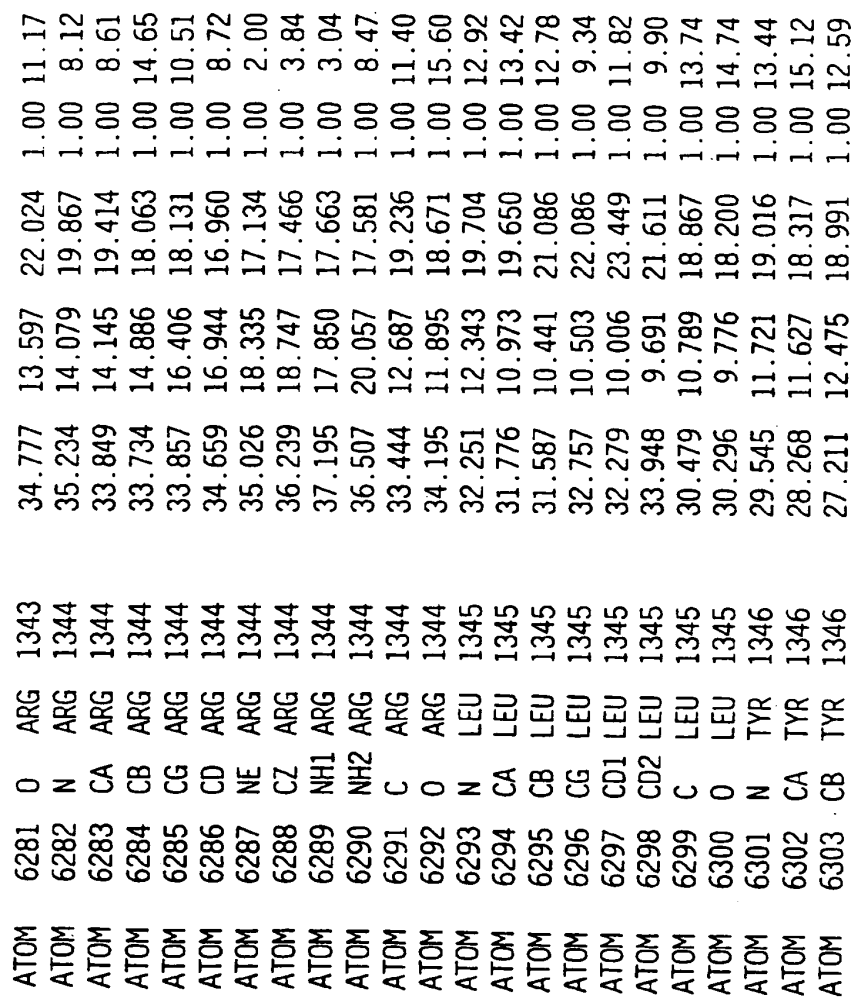
FIG.23.120

```
ATOM   6235  CA  ASN  1339      40.106  21.672  22.015  1.00 18.12
ATOM   6236  CB  ASN  1339      40.218  23.019  21.282  1.00  8.67
ATOM   6237  CG  ASN  1339      39.718  22.950  19.866  1.00  5.10
ATOM   6238  OD1 ASN  1339      40.490  22.743  18.946  1.00  8.82
ATOM   6239  ND2 ASN  1339      38.430  23.146  19.680  1.00  5.01
ATOM   6240  C   ASN  1339      40.875  20.581  21.247  1.00 14.35
ATOM   6241  O   ASN  1339      40.279  19.655  20.682  1.00 10.62
ATOM   6242  N   LEU  1340      42.199  20.685  21.285  1.00 13.18
ATOM   6243  CA  LEU  1340      43.110  19.745  20.646  1.00 16.72
ATOM   6244  CB  LEU  1340      44.563  20.126  20.961  1.00 13.44
ATOM   6245  CG  LEU  1340      45.659  19.179  20.460  1.00 12.01
ATOM   6246  CD1 LEU  1340      45.978  19.476  18.998  1.00 15.80
ATOM   6247  CD2 LEU  1340      46.917  19.367  21.274  1.00 15.88
ATOM   6248  C   LEU  1340      42.902  18.303  21.105  1.00 18.71
ATOM   6249  O   LEU  1340      42.970  17.374  20.301  1.00 18.27
ATOM   6250  N   GLN  1341      42.699  18.106  22.403  1.00 17.49
ATOM   6251  CA  GLN  1341      42.541  16.761  22.939  1.00 12.85
ATOM   6252  CB  GLN  1341      43.155  16.651  24.325  1.00 15.30
ATOM   6253  CG  GLN  1341      44.524  17.268  24.488  1.00 19.46
ATOM   6254  CD  GLN  1341      45.016  17.144  25.916  1.00 25.14
ATOM   6255  OE1 GLN  1341      44.551  17.844  26.827  1.00 25.07
ATOM   6256  NE2 GLN  1341      45.927  16.210  26.131  1.00 31.90
ATOM   6257  C   GLN  1341      41.110  16.307  23.032  1.00 14.53
```

FIG.23.121

```
ATOM   6258  O   GLN  1341      40.854  15.199  23.495  1.00 17.43
ATOM   6259  N   TYR  1342      40.171  17.146  22.624  1.00  9.28
ATOM   6260  CA  TYR  1342      38.778  16.771  22.700  1.00 10.17
ATOM   6261  CB  TYR  1342      37.897  17.952  22.384  1.00  6.11
ATOM   6262  CG  TYR  1342      36.485  17.736  22.814  1.00  2.40
ATOM   6263  CD1 TYR  1342      36.093  18.006  24.127  1.00  4.27
ATOM   6264  CE1 TYR  1342      34.761  17.852  24.531  1.00  4.78
ATOM   6265  CD2 TYR  1342      35.533  17.302  21.921  1.00  2.00
ATOM   6266  CE2 TYR  1342      34.200  17.136  22.312  1.00  3.49
ATOM   6267  CZ  TYR  1342      33.819  17.413  23.611  1.00  2.00
ATOM   6268  OH  TYR  1342      32.504  17.277  23.984  1.00  5.33
ATOM   6269  C   TYR  1342      38.416  15.643  21.766  1.00 13.26
ATOM   6270  O   TYR  1342      38.923  15.579  20.640  1.00 16.99
ATOM   6271  N   ARG  1343      37.515  14.769  22.212  1.00 14.41
ATOM   6272  CA  ARG  1343      37.065  13.677  21.377  1.00 13.13
ATOM   6273  CB  ARG  1343      37.434  12.310  21.974  1.00 21.72
ATOM   6274  CG  ARG  1343      37.145  11.155  21.023  1.00 29.33
ATOM   6275  CD  ARG  1343      37.482   9.801  21.614  1.00 36.24
ATOM   6276  NE  ARG  1343      37.233   8.708  20.665  1.00 41.97
ATOM   6277  CZ  ARG  1343      36.967   7.451  21.016  1.00 43.51
ATOM   6278  NH1 ARG  1343      36.894   7.112  22.293  1.00 43.48
ATOM   6279  NH2 ARG  1343      36.842   6.509  20.093  1.00 46.91
ATOM   6280  C   ARG  1343      35.579  13.754  21.111  1.00  9.94
```

FIG.23.122



```
ATOM   6281  O   ARG  1343      34.777  13.597  22.024  1.00 11.17
ATOM   6282  N   ARG  1344      35.234  14.079  19.867  1.00  8.12
ATOM   6283  CA  ARG  1344      33.849  14.145  19.414  1.00  8.61
ATOM   6284  CB  ARG  1344      33.734  14.886  18.063  1.00 14.65
ATOM   6285  CG  ARG  1344      33.857  16.406  18.131  1.00 10.51
ATOM   6286  CD  ARG  1344      34.659  16.944  16.960  1.00  8.72
ATOM   6287  NE  ARG  1344      35.026  18.335  17.134  1.00  2.00
ATOM   6288  CZ  ARG  1344      36.239  18.747  17.466  1.00  3.84
ATOM   6289  NH1 ARG  1344      37.195  17.850  17.663  1.00  3.04
ATOM   6290  NH2 ARG  1344      36.507  20.057  17.581  1.00  8.47
ATOM   6291  C   ARG  1344      33.444  12.687  19.236  1.00 11.40
ATOM   6292  O   ARG  1344      34.195  11.895  18.671  1.00 15.60
ATOM   6293  N   LEU  1345      32.251  12.343  19.704  1.00 12.92
ATOM   6294  CA  LEU  1345      31.776  10.973  19.650  1.00 13.42
ATOM   6295  CB  LEU  1345      31.587  10.441  21.086  1.00 12.78
ATOM   6296  CG  LEU  1345      32.757  10.503  22.086  1.00  9.34
ATOM   6297  CD1 LEU  1345      32.279  10.006  23.449  1.00 11.82
ATOM   6298  CD2 LEU  1345      33.948   9.691  21.611  1.00  9.90
ATOM   6299  C   LEU  1345      30.479  10.789  18.867  1.00 13.74
ATOM   6300  O   LEU  1345      30.296   9.776  18.200  1.00 14.74
ATOM   6301  N   TYR  1346      29.545  11.721  19.016  1.00 13.44
ATOM   6302  CA  TYR  1346      28.268  11.627  18.317  1.00 15.12
ATOM   6303  CB  TYR  1346      27.211  12.475  18.991  1.00 12.59
```

FIG.23.123

```
ATOM   6304  CG  TYR  1346      26.861  11.962  20.353  1.00 16.63
ATOM   6305  CD1 TYR  1346      27.387  12.551  21.500  1.00 15.96
ATOM   6306  CE1 TYR  1346      27.068  12.085  22.748  1.00 19.57
ATOM   6307  CD2 TYR  1346      26.010  10.883  20.496  1.00 19.19
ATOM   6308  CE2 TYR  1346      25.685  10.400  21.740  1.00 21.89
ATOM   6309  CZ  TYR  1346      26.214  11.006  22.870  1.00 22.13
ATOM   6310  OH  TYR  1346      25.859  10.544  24.116  1.00 25.59
ATOM   6311  C   TYR  1346      28.443  12.094  16.903  1.00 16.81
ATOM   6312  O   TYR  1346      29.268  12.957  16.631  1.00 21.14
ATOM   6313  N   ARG  1347      27.665  11.515  16.003  1.00 19.07
ATOM   6314  CA  ARG  1347      27.738  11.864  14.594  1.00 20.79
ATOM   6315  CB  ARG  1347      27.398  10.618  13.762  1.00 27.99
ATOM   6316  CG  ARG  1347      27.725  10.703  12.274  1.00 39.49
ATOM   6317  CD  ARG  1347      27.515   9.351  11.578  1.00 49.20
ATOM   6318  NE  ARG  1347      26.312   9.312  10.744  1.00 60.26
ATOM   6319  CZ  ARG  1347      25.070   9.200  11.216  1.00 68.75
ATOM   6320  NH1 ARG  1347      24.857   9.109  12.524  1.00 70.26
ATOM   6321  NH2 ARG  1347      24.031   9.202  10.383  1.00 74.59
ATOM   6322  C   ARG  1347      26.759  13.003  14.299  1.00 15.82
ATOM   6323  O   ARG  1347      27.036  13.865  13.471  1.00 16.50
ATOM   6324  N   SER  1348      25.653  13.011  15.042  1.00 15.40
ATOM   6325  CA  SER  1348      24.576  13.974  14.901  1.00 14.60
ATOM   6326  CB  SER  1348      23.741  13.638  13.634  1.00 14.11
```

FIG.23.124

ATOM	6327	OG	SER	1348	22.346	13.446	13.884	1.00	20.31
ATOM	6328	C	SER	1348	23.697	13.916	16.152	1.00	14.62
ATOM	6329	O	SER	1348	23.724	12.924	16.886	1.00	18.91
ATOM	6330	N	MET	1349	22.894	14.959	16.352	1.00	13.16
ATOM	6331	CA	MET	1349	21.990	15.092	17.496	1.00	13.39
ATOM	6332	CB	MET	1349	21.921	16.565	17.926	1.00	12.12
ATOM	6333	CG	MET	1349	23.222	17.083	18.548	1.00	9.38
ATOM	6334	SD	MET	1349	23.674	16.189	20.099	1.00	11.99
ATOM	6335	CE	MET	1349	25.015	15.158	19.578	1.00	7.72
ATOM	6336	C	MET	1349	20.581	14.577	17.239	1.00	12.37
ATOM	6337	O	MET	1349	19.670	14.796	18.058	1.00	13.03
ATOM	6338	N	ASN	1350	20.406	13.884	16.113	1.00	14.56
ATOM	6339	CA	ASN	1350	19.101	13.357	15.728	1.00	15.80
ATOM	6340	CB	ASN	1350	19.226	12.585	14.398	1.00	20.93
ATOM	6341	CG	ASN	1350	17.921	11.893	13.982	1.00	21.97
ATOM	6342	OD1	ASN	1350	17.728	10.709	14.274	1.00	25.95
ATOM	6343	ND2	ASN	1350	17.033	12.615	13.286	1.00	23.78
ATOM	6344	C	ASN	1350	18.439	12.511	16.827	1.00	16.55
ATOM	6345	O	ASN	1350	17.305	12.798	17.254	1.00	17.81
ATOM	6481	N	TYR	1367	17.962	28.227	16.494	1.00	6.02
ATOM	6482	CA	TYR	1367	17.931	29.500	15.804	1.00	5.74
ATOM	6483	CB	TYR	1367	17.436	30.624	16.737	1.00	10.60

FIG.23.125

```
ATOM   6484  CG  TYR  1367      18.328  30.911  17.917  1.00 10.03
ATOM   6485  CD1 TYR  1367      19.341  31.849  17.811  1.00  8.60
ATOM   6486  CE1 TYR  1367      20.232  32.054  18.823  1.00 10.34
ATOM   6487  CD2 TYR  1367      18.221  30.182  19.108  1.00  7.91
ATOM   6488  CE2 TYR  1367      19.128  30.382  20.143  1.00  6.03
ATOM   6489  CZ  TYR  1367      20.132  31.318  19.980  1.00 12.63
ATOM   6490  OH  TYR  1367      21.098  31.510  20.921  1.00 16.15
ATOM   6491  C   TYR  1367      19.292  29.774  15.204  1.00  6.67
ATOM   6492  O   TYR  1367      20.311  29.466  15.812  1.00  6.01
ATOM   6493  N   ASN  1368      19.309  30.270  13.976  1.00 10.44
ATOM   6494  CA  ASN  1368      20.576  30.519  13.293  1.00  7.58
ATOM   6495  CB  ASN  1368      20.793  29.503  12.151  1.00  3.77
ATOM   6496  CG  ASN  1368      21.153  28.108  12.640  1.00  4.12
ATOM   6497  OD1 ASN  1368      20.332  27.411  13.221  1.00  7.87
ATOM   6498  ND2 ASN  1368      22.363  27.668  12.328  1.00  3.22
ATOM   6499  C   ASN  1368      20.640  31.893  12.649  1.00  4.00
ATOM   6500  O   ASN  1368      19.684  32.329  12.027  1.00 11.97
ATOM   6501  N   GLY  1369      21.767  32.568  12.823  1.00  8.85
ATOM   6502  CA  GLY  1369      21.981  33.839  12.172  1.00  8.13
ATOM   6503  C   GLY  1369      22.323  33.430  10.751  1.00  7.52
ATOM   6504  O   GLY  1369      23.222  32.604  10.548  1.00  7.14
ATOM   6505  N   ASP  1370      21.615  33.989   9.775  1.00 12.01
ATOM   6506  CA  ASP  1370      21.809  33.609   8.370  1.00 10.99
```

FIG.23.126

ATOM	6507	CB	ASP	1370	20.514	33.855	7.603	1.00	8.82
ATOM	6508	CG	ASP	1370	20.165	35.330	7.489	1.00	7.50
ATOM	6509	OD1	ASP	1370	20.992	36.196	7.823	1.00	4.05
ATOM	6510	OD2	ASP	1370	19.057	35.624	7.018	1.00	5.18
ATOM	6511	C	ASP	1370	23.022	34.034	7.518	1.00	7.16
ATOM	6512	O	ASP	1370	23.037	33.741	6.316	1.00	9.67
ATOM	6513	N	VAL	1371	24.024	34.687	8.119	1.00	3.88
ATOM	6514	CA	VAL	1371	25.233	35.124	7.402	1.00	3.42
ATOM	6515	CB	VAL	1371	25.383	36.690	7.313	1.00	6.68
ATOM	6516	CG1	VAL	1371	24.090	37.309	6.845	1.00	5.56
ATOM	6517	CG2	VAL	1371	25.777	37.277	8.616	1.00	9.26
ATOM	6518	C	VAL	1371	26.483	34.489	8.001	1.00	3.95
ATOM	6519	O	VAL	1371	27.621	34.862	7.711	1.00	9.43
ATOM	6520	N	ASP	1372	26.236	33.509	8.853	1.00	4.54
ATOM	6521	CA	ASP	1372	27.281	32.743	9.500	1.00	7.15
ATOM	6522	CB	ASP	1372	26.713	32.129	10.782	1.00	5.20
ATOM	6523	CG	ASP	1372	27.638	31.126	11.410	1.00	2.00
ATOM	6524	OD1	ASP	1372	28.849	31.353	11.441	1.00	5.12
ATOM	6525	OD2	ASP	1372	27.129	30.089	11.879	1.00	9.13
ATOM	6526	C	ASP	1372	27.645	31.617	8.552	1.00	3.35
ATOM	6527	O	ASP	1372	26.777	31.086	7.858	1.00	8.14
ATOM	6528	N	MET	1373	28.918	31.234	8.573	1.00	4.20
ATOM	6529	CA	MET	1373	29.403	30.143	7.748	1.00	8.15

FIG.23.127

```
ATOM   6530  CB  MET  1373      30.465  30.657   6.771  1.00 12.00
ATOM   6531  CG  MET  1373      29.968  31.747   5.838  1.00  8.48
ATOM   6532  SD  MET  1373      31.081  32.014   4.499  1.00 11.70
ATOM   6533  CE  MET  1373      32.365  32.981   5.268  1.00  2.75
ATOM   6534  C   MET  1373      29.968  28.970   8.595  1.00 11.20
ATOM   6535  O   MET  1373      30.229  27.884   8.059  1.00 12.21
ATOM   6536  N   ALA  1374      30.157  29.194   9.905  1.00  9.28
ATOM   6537  CA  ALA  1374      30.671  28.157  10.802  1.00  5.98
ATOM   6538  CB  ALA  1374      31.216  28.764  12.090  1.00  3.14
ATOM   6539  C   ALA  1374      29.581  27.134  11.090  1.00  2.00
ATOM   6540  O   ALA  1374      29.851  25.953  11.134  1.00 10.17
ATOM   6541  N   CYS  1375      28.341  27.587  11.253  1.00  3.77
ATOM   6542  CA  CYS  1375      27.184  26.700  11.478  1.00  5.23
ATOM   6543  CB  CYS  1375      26.853  26.503  12.980  1.00  8.90
ATOM   6544  SG  CYS  1375      27.943  25.434  14.011  1.00 11.46
ATOM   6545  C   CYS  1375      26.005  27.348  10.742  1.00  7.20
ATOM   6546  O   CYS  1375      24.981  27.718  11.349  1.00  8.32
ATOM   6547  N   ASN  1376      26.155  27.491   9.427  1.00  7.19
ATOM   6548  CA  ASN  1376      25.137  28.123   8.581  1.00  5.23
ATOM   6549  CB  ASN  1376      25.499  28.012   7.093  1.00  4.07
ATOM   6550  CG  ASN  1376      25.125  26.652   6.471  1.00  5.32
ATOM   6551  OD1 ASN  1376      23.975  26.432   6.108  1.00  6.48
ATOM   6552  ND2 ASN  1376      26.112  25.771   6.307  1.00  3.48
```

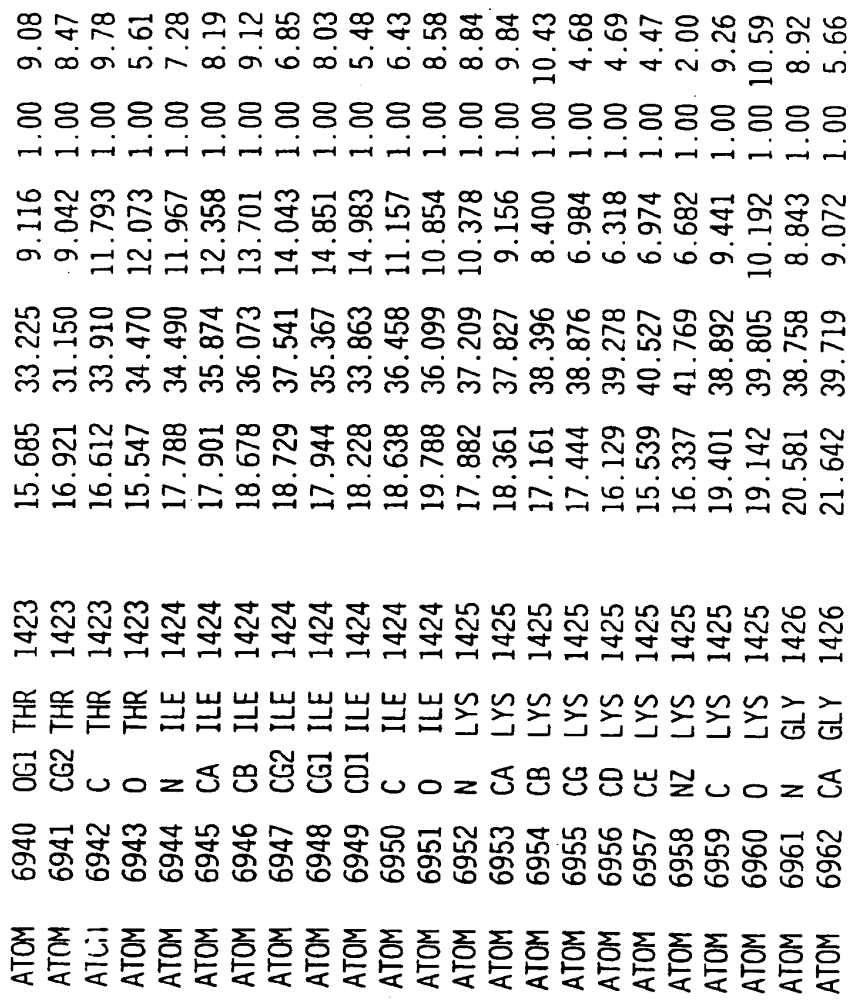
FIG.23.128

```
ATOM   6553  C   ASN 1376      23.715  27.649   8.852  1.00  7.03
ATOM   6554  O   ASN 1376      23.498  26.526   9.335  1.00 13.20
ATOM   6555  N   PHE 1377      22.758  28.557   8.652  1.00  9.98
ATOM   6556  CA  PHE 1377      21.356  28.276   8.888  1.00  7.71
ATOM   6557  CB  PHE 1377      20.517  29.524   8.587  1.00  7.80
ATOM   6558  CG  PHE 1377      20.270  29.745   7.098  1.00  9.44
ATOM   6559  CD1 PHE 1377      19.120  29.235   6.489  1.00 11.63
ATOM   6560  CD2 PHE 1377      21.236  30.354   6.287  1.00  5.43
ATOM   6561  CE1 PHE 1377      18.954  29.325   5.105  1.00  8.50
ATOM   6562  CE2 PHE 1377      21.059  30.438   4.906  1.00  2.70
ATOM   6563  CZ  PHE 1377      19.926  29.926   4.326  1.00  4.61
ATOM   6564  C   PHE 1377      20.782  27.095   8.076  1.00 11.99
ATOM   6565  O   PHE 1377      19.794  26.477   8.500  1.00 10.68
ATOM   6566  N   MET 1378      21.349  26.829   6.892  1.00 11.15
ATOM   6567  CA  MET 1378      20.817  25.778   6.019  1.00 13.98
ATOM   6568  CB  MET 1378      21.396  25.884   4.607  1.00 15.25
ATOM   6569  CG  MET 1378      20.775  24.872   3.654  1.00 17.89
ATOM   6570  SD  MET 1378      20.839  25.303   1.920  1.00 17.94
ATOM   6571  CE  MET 1378      19.396  26.394   1.807  1.00  2.03
ATOM   6572  C   MET 1378      21.026  24.390   6.580  1.00 10.20
ATOM   6573  O   MET 1378      20.097  23.583   6.589  1.00 16.11
ATOM   6574  N   GLY 1379      22.258  24.121   7.008  1.00 11.19
ATOM   6575  CA  GLY 1379      22.613  22.857   7.631  1.00 10.74
```

FIG.23.129

```
ATOM   6576  C   GLY  1379      21.704  22.588   8.817  1.00 11.28
ATOM   6577  O   GLY  1379      21.300  21.449   9.045  1.00 13.51
ATOM   6578  N   ASP  1380      21.358  23.631   9.566  1.00  8.03
ATOM   6579  CA  ASP  1380      20.472  23.448  10.695  1.00  8.63
ATOM   6580  CB  ASP  1380      20.692  24.475  11.794  1.00 11.80
ATOM   6581  CG  ASP  1380      21.752  24.031  12.784  1.00 10.38
ATOM   6582  OD1 ASP  1380      21.731  22.847  13.159  1.00 15.61
ATOM   6583  OD2 ASP  1380      22.613  24.842  13.171  1.00  9.23
ATOM   6584  C   ASP  1380      19.025  23.391  10.293  1.00  9.86
ATOM   6585  O   ASP  1380      18.205  22.786  11.002  1.00 14.03
ATOM   6586  N   GLU  1381      18.687  23.980   9.152  1.00  8.46
ATOM   6587  CA  GLU  1381      17.307  23.898   8.721  1.00  5.09
ATOM   6588  CB  GLU  1381      16.971  24.937   7.682  1.00  8.59
ATOM   6589  CG  GLU  1381      15.495  24.966   7.476  1.00  4.08
ATOM   6590  CD  GLU  1381      15.018  26.242   6.827  1.00  4.49
ATOM   6591  OE1 GLU  1381      15.863  27.054   6.384  1.00 11.09
ATOM   6592  OE2 GLU  1381      13.781  26.417   6.768  1.00 11.03
ATOM   6593  C   GLU  1381      17.066  22.517   8.156  1.00  6.96
ATOM   6594  O   GLU  1381      15.987  21.954   8.319  1.00 12.20
==========================================================================
ATOM   6937  N   THR  1423      15.464  31.718  11.756  1.00 10.99
ATOM   6938  CA  THR  1423      16.651  32.454  11.282  1.00 10.26
ATOM   6939  CB  THR  1423      16.798  32.528   9.688  1.00  7.48
```

FIG.23.130



ATOM	6940	OG1	THR	1423	15.685	33.225	9.116	1.00	9.08
ATOM	6941	CG2	THR	1423	16.921	31.150	9.042	1.00	8.47
ATOM	6942	C	THR	1423	16.612	33.910	11.793	1.00	9.78
ATOM	6943	O	THR	1423	15.547	34.470	12.073	1.00	5.61
ATOM	6944	N	ILE	1424	17.788	34.490	11.967	1.00	7.28
ATOM	6945	CA	ILE	1424	17.901	35.874	12.358	1.00	8.19
ATOM	6946	CB	ILE	1424	18.678	36.073	13.701	1.00	9.12
ATOM	6947	CG2	ILE	1424	18.729	37.541	14.043	1.00	6.85
ATOM	6948	CG1	ILE	1424	17.944	35.367	14.851	1.00	8.03
ATOM	6949	CD1	ILE	1424	18.228	33.863	14.983	1.00	5.48
ATOM	6950	C	ILE	1424	18.638	36.458	11.157	1.00	6.43
ATOM	6951	O	ILE	1424	19.788	36.099	10.854	1.00	8.58
ATOM	6952	N	LYS	1425	17.882	37.209	10.378	1.00	8.84
ATOM	6953	CA	LYS	1425	18.361	37.827	9.156	1.00	9.84
ATOM	6954	CB	LYS	1425	17.161	38.396	8.400	1.00	10.43
ATOM	6955	CG	LYS	1425	17.444	38.876	6.984	1.00	4.68
ATOM	6956	CD	LYS	1425	16.129	39.278	6.318	1.00	4.69
ATOM	6957	CE	LYS	1425	15.539	40.527	6.974	1.00	4.47
ATOM	6958	NZ	LYS	1425	16.337	41.769	6.682	1.00	2.00
ATOM	6959	C	LYS	1425	19.401	38.892	9.441	1.00	9.26
ATOM	6960	O	LYS	1425	19.142	39.805	10.192	1.00	10.59
ATOM	6961	N	GLY	1426	20.581	38.758	8.843	1.00	8.92
ATOM	6962	CA	GLY	1426	21.642	39.719	9.072	1.00	5.66

FIG.23.131

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ATOM   6963  C   GLY  1426      22.575  39.389  10.226  1.00   6.86
ATOM   6964  O   GLY  1426      23.549  40.108  10.446  1.00   7.21
ATOM   6965  N   ALA  1427      22.297  38.300  10.952  1.00   7.01
ATOM   6966  CA  ALA  1427      23.114  37.877  12.094  1.00   5.23
ATOM   6967  CB  ALA  1427      22.208  37.415  13.248  1.00   4.59
ATOM   6968  C   ALA  1427      24.104  36.773  11.743  1.00   7.23
ATOM   6969  O   ALA  1427      23.833  35.937  10.880  1.00  11.45
ATOM   6970  N   GLY  1428      25.256  36.798  12.392  1.00   4.17
ATOM   6971  CA  GLY  1428      26.266  35.791  12.192  1.00   2.76
ATOM   6972  C   GLY  1428      26.173  34.717  13.267  1.00   5.55
ATOM   6973  O   GLY  1428      25.132  34.512  13.862  1.00   7.07
ATOM   6974  N   HIS  1429      27.299  34.087  13.565  1.00   8.47
ATOM   6975  CA  HIS  1429      27.393  33.001  14.537  1.00   9.30
ATOM   6976  CB  HIS  1429      28.834  32.509  14.572  1.00   7.05
ATOM   6977  CG  HIS  1429      28.976  31.073  14.968  1.00   8.37
ATOM   6978  CD2 HIS  1429      29.797  30.470  15.854  1.00   6.41
ATOM   6979  ND1 HIS  1429      28.242  30.067  14.384  1.00   8.28
ATOM   6980  CE1 HIS  1429      28.614  28.905  14.882  1.00  11.00
ATOM   6981  NE2 HIS  1429      29.555  29.124  15.777  1.00   4.85
ATOM   6982  C   HIS  1429      26.943  33.354  15.959  1.00  13.88
ATOM   6983  O   HIS  1429      26.383  32.525  16.704  1.00  11.14
ATOM   6984  N   MET  1430      27.286  34.566  16.348  1.00  12.42
ATOM   6985  CA  MET  1430      26.951  35.087  17.647  1.00  10.27
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FIG.23.132

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ATOM   6986  CB  MET  1430      28.187  35.741  18.212  1.00 11.88
ATOM   6987  CG  MET  1430      29.358  34.801  18.042  1.00 12.77
ATOM   6988  SD  MET  1430      30.824  35.317  18.863  1.00 23.27
ATOM   6989  CE  MET  1430      30.210  35.566  20.570  1.00 25.45
ATOM   6990  C   MET  1430      25.809  36.055  17.485  1.00  7.49
ATOM   6991  O   MET  1430      25.971  37.267  17.535  1.00 10.99
ATOM   6992  N   VAL  1431      24.641  35.475  17.250  1.00  9.86
ATOM   6993  CA  VAL  1431      23.394  36.183  17.039  1.00  9.97
ATOM   6994  CB  VAL  1431      22.229  35.166  17.026  1.00 10.82
ATOM   6995  CG1 VAL  1431      20.891  35.873  17.075  1.00 11.53
ATOM   6996  CG2 VAL  1431      22.337  34.259  15.809  1.00  8.28
ATOM   6997  C   VAL  1431      23.113  37.337  18.033  1.00 13.86
ATOM   6998  O   VAL  1431      22.727  38.431  17.606  1.00 15.08
ATOM   6999  N   PRO  1432      23.297  37.113  19.360  1.00 15.76
ATOM   7000  CD  PRO  1432      23.474  35.836  20.085  1.00 10.92
ATOM   7001  CA  PRO  1432      23.036  38.201  20.320  1.00 14.93
ATOM   7002  CB  PRO  1432      23.263  37.520  21.671  1.00 13.69
ATOM   7003  CG  PRO  1432      22.788  36.124  21.401  1.00 16.54
ATOM   7004  C   PRO  1432      23.947  39.416  20.126  1.00 13.31
ATOM   7005  O   PRO  1432      23.548  40.547  20.377  1.00 16.11
ATOM   7006  N   THR  1433      25.170  39.170  19.681  1.00 10.45
ATOM   7007  CA  THR  1433      26.122  40.229  19.430  1.00  7.78
ATOM   7008  CB  THR  1433      27.521  39.637  19.244  1.00  7.33
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FIG.23.133

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ATOM   7009  OG1 THR  1433      27.908  38.956  20.438  1.00 13.92
ATOM   7010  CG2 THR  1433      28.558  40.704  18.941  1.00  8.45
ATOM   7011  C   THR  1433      25.733  41.053  18.184  1.00 11.42
ATOM   7012  O   THR  1433      25.914  42.266  18.155  1.00 15.01
ATOM   7013  N   ASP  1434      25.178  40.403  17.164  1.00 10.90
ATOM   7014  CA  ASP  1434      24.835  41.087  15.920  1.00  9.93
ATOM   7015  CB  ASP  1434      24.967  40.115  14.735  1.00 10.58
ATOM   7016  CG  ASP  1434      26.350  39.494  14.653  1.00 11.03
ATOM   7017  OD1 ASP  1434      27.322  40.210  14.942  1.00 15.21
ATOM   7018  OD2 ASP  1434      26.479  38.295  14.314  1.00 15.54
ATOM   7019  C   ASP  1434      23.463  41.715  15.901  1.00  9.56
ATOM   7020  O   ASP  1434      23.286  42.793  15.373  1.00 18.13
ATOM   7021  N   LYS  1435      22.494  41.013  16.462  1.00 11.01
ATOM   7022  CA  LYS  1435      21.119  41.473  16.508  1.00 13.58
ATOM   7023  CB  LYS  1435      20.267  40.588  15.585  1.00 12.74
ATOM   7024  CG  LYS  1435      20.720  40.593  14.154  1.00 12.81
ATOM   7025  CD  LYS  1435      20.393  41.945  13.557  1.00 12.44
ATOM   7026  CE  LYS  1435      21.074  42.141  12.231  1.00 14.51
ATOM   7027  NZ  LYS  1435      20.667  43.427  11.646  1.00  8.06
ATOM   7028  C   LYS  1435      20.605  41.372  17.945  1.00 13.46
ATOM   7029  O   LYS  1435      19.766  40.501  18.248  1.00 16.10
ATOM   7030  N   PRO  1436      21.052  42.289  18.836  1.00 12.75
ATOM   7031  CD  PRO  1436      22.003  43.380  18.563  1.00  7.82
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FIG.23.134

```
ATOM   7032  CA  PRO  1436      20.656  42.322  20.263  1.00 12.46
ATOM   7033  CB  PRO  1436      21.350  43.579  20.791  1.00 11.07
ATOM   7034  CG  PRO  1436      22.573  43.652  19.947  1.00 10.88
ATOM   7035  C   PRO  1436      19.157  42.354  20.520  1.00 11.93
ATOM   7036  O   PRO  1436      18.640  41.486  21.204  1.00 12.78
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FIG.23.135

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/17325

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07K 1/14, 14/435
US CL : 530/350, 412, 418, 421
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350, 412, 418, 421

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN, BIOSIS, MEDLINE, EMABSE, WPIDS
search terms: protective protein, cathepsin, crystal?,cathepsin`a, ppca,rudenko, hpp

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KAZAKOVA et al. Crystallization of Cathepsin D. Biochem. Biophys. Res. Comm., 1976. Vol. 72, No. 2, pages 747-752.	1-4
A	FUSEK et al. Purification and Crystallization of Human Cathepsin D. 1992. Vol. 226, pages 555-557.	1-4
X, P	RUDENKO et al. Three-dimensional structure of the human 'protective protein': structure of the precursor form suggests a complex activation mechanism. 15 November 1995. Vol. 3, No. 11, pages 1249-1259, especially page 1257, column 1.	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 MARCH 1997	03 APR 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CHRISTINE SAOUD Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/17325

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/17325

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-4, sharing the inventive concept of methods of crystallizing PPCA or pPPCA.

Group II, claims 5 and 18, sharing the inventive concept of PPCA protein.

Group III, claims 6-11, sharing the inventive concept of a method of providing an atomic model of PPCA.

Group IV, claims 12-13 and 15-16, sharing the inventive concept of a method of providing an atomic model of a ligand for PPCA.

Group V, claims 14 and 17, sharing the inventive concept of a ligand for PPCA.

The inventions listed as Groups I-V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept. The "special technical features" means those technical features that define a contribution over the prior art. (See PCT Rule 13.2.) Because PPCA was known in the prior art (see description at page 1, lines 16-18), it cannot form the basis of unity of invention. Therefore, the main invention which forms a single inventive concept is Group I, claims 1-4, which is a method of crystallizing. Group II has the inventive concept of a PPCA protein, Group III has the inventive concept of a method of providing an atomic model of PPCA, Group IV had the inventive concept of providing an atomic model of a ligand for PPCA and Group V has the inventive concept of a ligand for PPCA; none of these Groups share the special technical of Group I therefore, unity of invention is lacking.